Changing perspectives on insomnia and depression

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CHANGING PERSPECTIVES ON INSOMNIA AND DEPRESSION: FROM SYMPTOMS TO SYSTEM

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COLOPHON

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CHANGING PERSPECTIVES ON INSOMNIA AND DEPRESSION: FROM SYMPTOMS TO SYSTEM

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CONTENTS

1 INTRODUCTION

1.1 INSOMNIA

1.1.1 *insomnia in society: then and now*

Sleep, and the lack thereof, have been valued differently throughout history. Plato, for example, considered minimal sleep necessary, but long sleep unsophisticated as "who sleeps is of no value, as a dead body" [1]. This tension between sleep and productivity was persistent. In the nineteenth century, Thomas Edison, inventor of the light bulb, was convinced that sleep was merely "a bad habit" that was instantiated by the lack of artificial light [2].

The tight relationship between sleep and activity is still captured in the dictionary, where *sleep* is defined as inactivity; the adjective sleep*less* can be used to refer to something that is constantly active or moving; and sleeplessness, or insomnia, is defined by the absence and inability to sleep [3].

The sole focus on insomnia in relationship to activity obscures some very important concepts about insomnia. First, it characterizes insomnia only in relation to sleep *quantity*. This is a common misperception; insomnia is not simply the absence of sleep quantity, but the absence of sleep *quality*.

Second, insomnia goes beyond the mere absence of sleep as it can have a profound impact on (mental) health. Already in the beginning of medicine Hippocrates recognized sleep to be one of six factors to promote health and noted that: "A disease in which sleep causes distress is a deadly one; but if sleep is beneficial, the disease is not deadly" [4].

Finally, also to the sufferer of insomnia, insomnia is much more than just the absence of sleep. From ancient Greece until today; books, poems, and memoirs have been dedicated to the topic of sleeplessness and its effect on daily lives and (mental) health. Insomnia remains an intriguing topic in literary work today. Last year, Marina Benjamin carefully described the suffering of insomnia and explained that it is more than "just a state of sleeplessness, a matter of negatives. It involves the active pursuit of sleep. It is a state of longing" [5].

All that has been written on sleeplessness, while various in focus, has one thing in common that forms an important premise for this thesis: insomnia goes well beyond sleep itself.

1.1.2 *insomnia today: prevalence and consequence*

One third of the population is dissatisfied with their sleep and report insomnia *complaints* as difficulty initiating sleep, difficulty maintaining sleep, or early

morning awakening [6]. For one in every ten adults these complaints persist at least three nights a week for at least three consecutive months, despite adequate sleep opportunity; result in impaired daytime functioning; and are not fully explained by another mental or sleep disorder. This 10% of the population meets the criteria for insomnia *disorder* [7], making insomnia the second-most prevalent mental disorder today [8].

The high prevalence has brought about an increasing interest in insomnia – scientifically, publicly, and commercially. In the last nine years, scientific output that included 'insomnia' was more than in the previous 20 years combined[1]; there are over a billion hits for the Google search term 'how to sleep better'; and some companies started to provide financial rewards to their co-workers to stimulate more sleep[2], in the hope their productivity goes up [9].

This heightened awareness on the importance of *sleep* is brought about by an increased understanding of the possible detrimental effects of sleep*less*ness. Sleep complaints can result in daytime problems such as fatigue, concentration problems, and mood disturbances – which, in turn, can result in work absenteeism and productivity loss. Insomnia can thereby greatly impair both physical and mental quality of life [10,11]. In addition, the work-related effects are estimated to be the largest economic consequence of insomnia [12], highlighting the impact of sleep problems for both the individual and society as a whole.

Enduring sleep problems are concurrently and prospectively associated with many mental and medical disorders. Insomnia often co-occurs with different psychiatric disorders such as anxiety and ADHD [13], is identified as a key determinant of the trajectories in different clinical populations [14,15], and increases the risk for medical disorders as diabetes [16] and cardiovascular disease [17].

Crucially, insomnia is found to be key to depression – with 300 million sufferers worldwide the largest mental health problem to date [18] and a major contributor to the global burden of disease [19]. Prospectively, insomnia is found to increase the risk of depression [20], and concurrently, around 80% of the people suffering from depression also report insomnia complaints [21].

Insomnia is thus not only highly prevalent itself, bringing about its own negative consequences; it is moreover associated to the onset and course of various medical and mental health problems, of which depression is the most common. Despite our increased understanding of these possible aversive consequences, little is yet known about the mechanisms underlying insomnia. Who are the people suffering from insomnia? What do they have in common, and how do they differ? Why do some continue to develop a depression, while others do not?

1 Pubmed search on 'insomnia' between 2010-2019 gave 10412 results, whereas between 1990-2009 there were 8045 results.

2 Note that again such reward systems only focus on sleep *quantity* and not sleep *quality*, reflecting a common misperception that insomnia is defined by sleep quantity.

Such an understanding is essential to begin to unravel the *underlying mechanisms* of insomnia in order to develop personalized *treatments*, *identify* individuals at risk, and *prevent* the onset of other disorders such as depression.

1.1.3 *insomnia heterogeneity*

Although the pathophysiology and mechanisms underlying insomnia disorder are still largely unknown, different perspectives have been postulated on the role of biological, psychological, and societal factors. The role of these factors can generally be classified into *predisposing*, *precipitating*, and *perpetuating* factors; where predisposing factors relate to the vulnerability to develop insomnia, precipitating factors form the trigger for an acute episode of insomnia, and perpetuating factors maintain the disorder.

Across biology, sociology and psychology, different characteristics have been identified: for instance, biological differences in genetic make-up [22] and hyperarousal [23]; societal factors such as socio-economic-status [24] and educational attainment [25]; and psychological differences in temperament and personality [26] – all have been associated to insomnia.

Nevertheless, it has proven difficult to pinpoint characteristics that are *consistently* related to insomnia across multiple studies and multiple research groups [27]. These inconsistencies signal possible heterogeneity due to the existence of different subtypes of insomnia disorder. Rather than one homogeneous disorder with a single underlying pathophysiology, insomnia could represent different subtypes, each with its own etiology. If such subtypes of insomnia exist, identification of these subtypes is crucial to begin to understand the underlying mechanisms of insomnia.

This recognition has over the years led to the proposition of many different subtypes of insomnia, defined by, for example, the most dominant sleep complaint (e.g., sleep onset insomnia for those suffering from difficulties falling asleep), the age of onset (e.g., idiopathic insomnia for those whose insomnia started in early childhood), or acquired sleep-preventing associations (e.g., psychophysiological insomnia for those who report conditioned worry and arousal in relation to bed). Although the proposed subtypes captured different aspects, they all had one thing in common: they were defined by committees and health care professionals, resulting in eminence- rather than evidence-based subtypes that most often related to sleep itself.

Unfortunately, none of these eminence-based, 'top-down' proposed subtypes demonstrated to be sufficiently reliable to capture more homogeneous subtypes of insomnia disorder [28]; which has led major nosologies to discard them from clinical classifications. Heterogeneity thus prevails and with it the importance of finding ways to successfully reduce insomnia heterogeneity.

Possibly, the top-down focus on heterogeneity in sleep-related characteristics has been too narrow. Instead, heterogeneity in predisposing or perpetuating factors that are not directly related to sleep but of relevance to insomnia

could perhaps capture more stable subtypes of insomnia. Moreover, rather than considering these factors in isolation, investigating them in concert might provide new avenues to capture the heterogeneity in insomnia.

1.1.4 *insomnia as a complex system*

Alternatively, insomnia disorder might be seen as a complex system, in which the *constellation* of different sets of factors – such as personality, perfectionism, affect, and life history – capture the vulnerability to develop and maintain the disorder. Instead of evaluating each factor in isolation, complex systems offer an integrative account that focuses on the interplay between factors [29]. Specifically, within this complex system, insomnia could be conceptualised as a stability landscape with two attractor states, of which one represents healthy sleep, and the other represents disturbed sleep. This idea of stable attractor states within complex systems has been described for numerous systems; from ecosystems [30] and financial markets [31] to depression [32,33].

The conceptualization of insomnia as a complex system allows for new ways to represent the disorder (i.e., as stable states) and to integrate the potential role of predisposing, precipitating, and perpetuating factors. Depending on the shape of the stability landscape, an individual will be more or less vulnerable to transition from one stable state to the other [34] – i.e., from healthy sleep into disturbed sleep. Predisposing factors could influence the shape of this landscape, thereby affecting the vulnerability of an individual to develop insomnia. Triggered by a precipitating factor, such as the loss of a loved one, or other major life events, the system can transition towards the unhealthy state of disturbed sleep. Subsequently, perpetuating factors determine whether the system will be locked into this state – ultimately resulting in an insomnia *disorder* – or whether the system will transition back into the healthy sleep state, causing the insomnia *complaints* to abate.

Crucially, from this perspective, the heterogeneity in insomnia does not need to relate to the sleep disturbances themselves. In the disordered attractor state, similar sleep complaints can be maintained by different sets of perpetuating factors. It might be the complex interplay between such factors that determine the context in which the insomnia complaints occur and are maintained.

One important aim of this thesis is to investigate whether insomnia comes in different subtypes that are related to traits of affect and personality, and life history, rather than in specific sleep complaints.

In order to accomplish this, we first had to identify the characteristics that could be relevant to the system of insomnia [27]. The identified characteristics were implemented in the Netherlands Sleep Registry, an online platform that allows for a large-scale multivariate assessment: between September 2010 and June 2016 over 10,000 participants completed more than half a million (sub)scales.

We continue in chapter 2 by exploring how personality – one of the identified characteristics that might be relevant to the system of insomnia – relates to different insomnia complaints spanning both nocturnal sleep disturbances and their daytime consequences.

In chapter 3 we address the key research question whether insomnia subtypes are reflected in life history and traits of affect and personality by conducting a large-scale data-driven analyses. We follow up on the identified subtypes of insomnia disorder by assessing their stability over time, and by thoroughly investigating their clinical utility.

1.2 INSOMNIA AND DEPRESSION

To disentangle insomnia disorder into more homogeneous subtypes offers a number of promising avenues. Future studies can then target homogeneous subtype samples to reveal differential mechanisms, and personalize and optimize treatments. In addition, and of particular interest for the remainder of this thesis, subtyping could provide new opportunities to identify the people with insomnia that run the highest risk of depression, thereby opening up possibilities for prevention and intervention of depression through insomnia.

Over the last twenty years, more than 600 research articles[3] have studied, reviewed, and theorized on the relationship between insomnia and depression. Although the precise link between the two disorders is still debated and investigated, some consistent empirical findings have emerged. Prospectively, insomnia is a major risk factor of depression, and it can been estimated that 13% of the people suffering from insomnia today, will have developed a depression within twelve months [20]. Concurrently, in people suffering from depression, insomnia is shown to impede remission [35], whereas successful treatment of insomnia can relieve depression symptomatology [36,37,38]. When the sleep disturbances are not treated directly, they often persist as residual symptoms [39] and increase the risk for relapse and recurrence [40,41].

Intuitively, insomnia and depression are clearly distinct. Whereas one is a disorder of the night, the other manifests itself during the day. But are these disorders clinically as distinct as they are semantically?

While insomnia is culturally defined in terms of the *night*, clinical insomnia is a 24-hour disorder spanning both night and *day*. The sleep disturbances at night should result in clinically significant distress during the day in order to meet the criteria for an insomnia disorder [7]. These daytime symptoms can vary from fatigue and loss of energy, to concentration problems and mood disturbances. Crucially, the daytime symptomatology of insomnia disorder is highly similar to the symptoms that belong to a depression diagnosis. Moreover, from the perspective of a depression diagnosis, sleep disturbances are listed as

3 Pubmed results for search term (relationship between insomnia and depression) OR (relationship between depression and insomnia) between 1999-2019.

a symptom of depression [7] and regarded as a critical feature of the diagnosis [42].

Considering these clinical definitions sheds another light on the empirically identified relationships between insomnia and depression. Could insomnia predict depression onset just because it is itself a symptom of depression? Is their high co-occurrence merely a reflection of their symptom overlap? Does the treatment of insomnia first affect the sleep complaints, after which the depression symptoms are alleviated? Or could it be that the treatment actually targets the depression directly? Ultimately, where does the insomnia disorder stop and the depression disorder begin?

1.2.1 *insomnia and depression as a system of symptoms*

At the diagnostic symptom level, these questions can only be answered if we specifically focus on the symptoms and their interactions. Such a shift in focus from the disorders as constructs to their symptoms and their interrelations is rooted in the *network theory of mental disorder* [43]. This theory postulates that mental disorders arise from the direct interactions between symptoms. Crucially, this conceptualization opens up the possibility to investigate symptom interactions that cut across the border of originally defined, discrete disorders – providing a new perspective to take the overlapping symptomatology between insomnia and depression into account [44].

In chapters 4 and 5 we adopt the network approach to investigate the prospective and concurrent relationship between insomnia and depression at the, more detailed, symptom level.

In chapter 4 we investigate whether insomnia can indeed be considered a risk factor of depression, if we take their symptom overlap into account. Investigating insomnia and depression from a network perspective does not in itself elucidate the risk factors of depression. We therefore apply a novel method for symptom network analysis [45], which we call Network Outcome Analysis (NOA), to answer this pressing need.

In a similar way, in chapter 5 we aim to disentangle the treatment effect of cognitive behavioural therapy for insomnia on both insomnia and depression symptoms. We introduce an innovation to the network analysis, coined Network Intervention Analysis (NIA), that incorporates 'treatment allocation' as a variable into the network. By deconstructing insomnia and depression into their associated sets of symptoms, we can reveal the symptom-specific, sequential treatment effects over time.

1.3 BEYOND INSOMNIA AND DEPRESSION

1.3.1 *community structure psychopathology*

The overlapping symptomatology that is observed in insomnia and depression is exemplar, yet occurs throughout current diagnostic nosologies. The network theory of mental disorders offers a unique framework from which these overlapping symptom patterns can be interpreted and explained. Rather than distinct underlying disorders, the symptoms and their interactions are the constituents of the disorders. Placing the symptom-to-symptom relations at the heart of mental disorders allows to re-examine mental disorders in terms of the role of specific symptoms and their interrelations. What symptoms are at the core of a disorder (i.e., hallmark symptoms)? What different symptom patterns do we observe (i.e., heterogeneity)? How do symptoms interact across the borders of currently defined disorders (i.e., comorbidity)?

While these questions follow logically from the network theory of mental disorders, most empirical network studies focused on one or two disorders, defined by and limited to its diagnostic boundaries. Comorbidity, one of the main clinical phenomena that the network theory can account for by overlapping symptoms and cross-diagnostic symptom interactions [46], is often investigated for just two disorders: anxiety and depression [47], depression and OCD [48], OCD and autism [49] – thereby obscuring the more global structure in psychopathology.

In a collaborative project, we investigate this global structure of psychopathology across many different disorders by focusing on the symptoms and their interrelations (chapter 6). Using community detection, a data-driven and bottom-up way to identify clusters, we study the community structure among psychopathology symptoms, allowing us to review the clinical concepts of hallmark symptoms, heterogeneity, and comorbidity from a network perspective.

1.3.2 *community structure in attention deficit hyperactivity disorder*

Community detection aims to find structure within complex systems that are represented as networks. In chapter 6 on psychopathology, for example, the nodes represent symptoms and the edges represent the co-occurrence of symptoms in a population. Structure within such complex systems is identified as the organization of nodes (e.g., symptoms) into clusters, where nodes that belong to the same cluster are more strongly connected (e.g., symptoms that co-occur more often) than nodes that belong to different clusters [50].

The identification of structure within complex systems is not limited to nodes that represent symptoms. Many different complex systems can be represented as networks, and community detection algorithms are agnostic as to what the network represents. In a final project, we investigate structure among children with attention deficit hyperactivity disorder (ADHD).

ADHD, just like insomnia, is characterised by heterogeneity and different symptom patterns are all classified as ADHD [51]. In a seminal study, Karalunas and colleagues used community detection to identify subgroups of ADHD based on their temperament ratings [52]. Here, the nodes represent children, and the edges represent the correlation among their scoring pattern of different temperament items. This way, the scoring pattern is pivotal to the identification of groups; children whose scoring *pattern* is more alike, will have stronger links and will thus a higher chance to belong to the same subgroup. Using community detection algorithms, Karalunas et al. found structure in this network that captured different subtypes of ADHD [52]. In a final collaborative project, we adopt their approach and investigate whether we can identify similar subtypes of ADHD using personality ratings (chapter 7). This project thus unites two major lines of research within this dissertation: the exploration of heterogeneity beyond just symptom patterns on the one hand (cf. chapter 3), and the use of community detection to find structure within this system on the other hand (cf. chapter 6).

1.4 THESIS OUTLINE

Who are the people suffering from insomnia? What do they have in common, and how do they differ? Why do some continue to develop a depression, while others do not? These series of questions form the basis for the research that has been conducted in this thesis. In the first part of this thesis (chapters 2 and 3) we aim to unravel the heterogeneity that is observed in insomnia. We continue to disentangle the relationship between insomnia depression, both prospectively and concurrently, in the second part (chapters 4 and 5). In the third part (chapters 6 and 7) we depart from insomnia and depression to investigate structure in psychopathology in general, and in ADHD in particular. Finally, in the discussion in chapter 8 we come back to the questions that lie at the core of this thesis and integrate the results from a clinical, methodological, and theoretical stance point.

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Part I

INSOMNIA

It appears that every man's insomnia is as different from his neighbours as are their daytime hope and aspirations.

— F. Scott Fitzgerald, "The Crack-Up"

2 INSOMNIA AND PERSONALITY

ABSTRACT

Studies on personality traits and insomnia have remained inconclusive about which traits show the most direct associations with insomnia severity. It has moreover hardly been explored how traits relate to specific characteristics of insomnia. We here used network analysis in a large sample (N=2089) to obtain an integrated view on the associations of personality traits with both overall insomnia severity and different insomnia characteristics, while distinguishing direct from indirect associations. We first estimated a network describing the associations among the five factor model personality traits and overall insomnia severity. Overall insomnia severity was associated with neuroticism, agreeableness, and openness. Subsequently, we estimated a separate network describing the associations among the personality traits and each of the seven individual items of the Insomnia Severity Index. This revealed relatively separate clusters of daytime and nocturnal insomnia complaints, that both contributed to dissatisfaction with sleep, and were both most directly associated with neuroticism and conscientiousness. The approach revealed the strongest direct associations between personality traits and the severity of different insomnia characteristics and overall insomnia severity. Differentiating them from indirect associations identified the targets for improving Cognitive Behavioral Therapy for insomnia with the highest probability of effectively changing the network of associated complaints.

2.1 INTRODUCTION

Insomnia is a common burden in the general population [1,2]. Insomnia disorder can be diagnosed if subjective problems with initiating sleep, maintaining sleep, or waking up too early occur at least three nights a week, persist for at least three months, and are accompanied by at least one form of subjective daytime impairments like fatigue, malaise, or difficulties with concentration [3]. The diagnosis of insomnia disorder thus requires the presence of both nocturnal and daytime complaints. Although the causes of insomnia are still poorly understood [4], a prevailing theory by Spielman et al. suggests the involvement of three types of factors [5]: premorbid predispositions, precipitating factors,

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and perpetuating factors. It has been suggested that certain personality traits may predispose to insomnia [6–10].

The dominant model of personality is the five-factor model (FFM), or the Big Five, and is based on a substantive body of evidence that found a five-factor solution to the correlations among personality characteristics [11]. The five personality traits are extraversion, agreeableness, conscientiousness, neuroticism, and openness. The study of personality traits in insomnia may provide clues about the underlying brain circuits involved in insomnia, because individual differences in personality traits are associated with individual differences in brain structure and brain function [12–14]. Some of the reported associations indeed seem relevant to insomnia, for example, both sleep vulnerability and introversion have been linked to low gray matter density in the orbitofrontal cortex [15–17].

Even though the association between personality traits and insomnia has been studied extensively [7–9,18–27], there is no conclusive consistency about which of the personality traits are most strongly associated with insomnia in a general adult population. Within the framework of the prevailing five-factor model (FFM) of personality [28], the most consistently reported finding in insomnia disorder is high neuroticism [7,8,18,20,22,25,26]. Several studies also suggested insomnia disorder to be associated with low conscientiousness, but showed that when all personality traits were simultaneously evaluated in a single regression model [18–20,22], this association appeared to be secondary to the inverse association of conscientiousness with neuroticism. Multi-collinearity of personality traits thus has to be considered in efforts to understand the complexity of direct and indirect relations between insomnia and personality traits.

A relatively unexplored aspect is whether specific symptoms of insomnia may be associated differentially with personality traits. Previous studies focused mostly on nocturnal symptoms of insomnia [18–20], or on a compound score [19,22]. Since insomnia is defined by both nocturnal and daytime aspects, it may be that some personality traits relate to nocturnal complaints, whereas others relate to daytime complaints. It could be more informative to perform an integrated analysis on how different symptoms of insomnia are associated with different personality traits.

Such an integrated analysis of how traits and symptoms are associated has shown to be feasible using network analysis. This method can simultaneously estimate partial correlations between all variables included—in our case all personality traits and insomnia symptoms measured—and visualizes them in a so-called concentration network graph. The graph shows all variables as nodes, and their partial correlations as connecting edges [29]. The relative strength of partial correlations can be represented by the length, color saturation, and width of the edges between each of the nodes. Network analysis has recently been introduced for psychometric data [30], including personality traits [29,31], and has found increasing popularity over the years [32].

The present study is, as far as we know, the first to apply network analyses on the data of a large sample of volunteers to obtain an integrated view on the associations of personality traits with overall insomnia severity as well as with different symptoms of insomnia. We estimated and visualized two concentration networks: one including the five personality traits and the Insomnia Severity Index (ISI) summary score; the other including the five personality traits and each of the seven individual ISI items.

2.2 MATERIALS AND METHODS

2.2.1 *Participants*

The data were obtained through the Netherlands Sleep Registry (NSR) [33]. The NSR is an internet platform that aims to asses a wide variety of traits across the general population, both good and bad sleepers [33], in order to create a psychometric database to facilitate research on traits that distinguish insomniacs from good sleepers. Participants of the NSR are unpaid volunteers that anonymously fill out as many different questionnaires as they wish, at a self-chosen place and time. Participants fill out each of the questionnaires once. Commitment is supported by online feedback, newsletters, and occasional voucher lotteries. For the present study, we included all participants that completed both the Insomnia Severity Index (ISI) [34], the Mini-International Personality Item Pool (Mini-IPIP) [35], and a questionnaire on demographics including age and sex. Participants younger than 18 were excluded. This resulted in a cross-sectional sample of 2089 volunteers (1573 females, 75.3%), with an age range of 18 to 84 years of age (Mean age 51.7$\pm$13.6). The questionnaires were filled out between May 2012 and October 2016. The median time difference between filling out ISI and Mini-IPIP was 7.4 months.

The Medical Ethical Committee of the Academic Medical Center of the University of Amsterdam (29 September 2009, 09.17.1396) as well as the Central Committee on Research Involving Human Subjects (CCMO, 14 December 2011, CCMO11.1813/GK/jt), The Hague, the Netherlands, approved of unsigned informed consent, because of the voluntary and anonymous nature of participation and lack of any intervention or behavioral constraint.

2.2.2 *Materials*

MINI-IPIP The 20-item Mini-IPIP [35] assesses the Big Five personality traits of neuroticism, conscientiousness, agreeableness, extraversion, and openness to experiences. Participants are asked to rate how accurate brief statements describe themselves, using a five-point Likert scale ranging from 1 (very inaccurate) to 5 (very accurate).

151 The Insomnia Severity Scale (ISI) is a seven-item scale that addresses aspects of insomnia [34]. Each question uses a five-point Likert scale, ranging from 0 to 4. The first three questions assess the three main sleep complaints: difficulty initiating sleep (DIS), difficulty maintaining sleep (DMS) and early morning awakening (EMA). Questions 4–7 assess respectively dissatisfaction with sleep (Dissat), interference with daily functioning (IDF), how noticeable sleep problems impair quality of life (NIQoL), and worry about sleep (Worry). The compound score is a simple sum score of all items, resulting in a score ranging from 0 to 28.

2.2.3 *Statistical analysis*

To estimate and visualize the concentration network of associations between the five personality traits and the Insomnia Severity Index (ISI) summary score, partial correlations were calculated between each of the six variables. The partial correlation among two variables represents the strength of the direct association between these variables, while taking all the other variables into account. The networks of the partial correlations thus represent the unique association between any two variables, that cannot be explained by their common associations with other variables [29]. As such, the network structure highlights possible pathways of influence: unrelated variables cannot directly influence each other, while the presence of a direct association indicates a potential causal pathway between two variables. To minimize spurious associations due to sampling error, we applied Least Absolute Shrinkage and Selection Operator (LASSO) regularization. This procedure controls for false-positive associations and retrieves only the most robust associations. Therefore, the included associations are very likely to play an important role in the network architecture (see Epskamp and Fried [36] for more information).

To visualize the concentration networks, each of the six variables is shown as a node, connected by edges. The edges in the network represent the partial correlations between variables that were estimated by the network model using LASSO regularization [29]. Green edges correspond to positive partial correlations, while red edges correspond to negative partial correlations. In addition, both the edge width and color saturation are scaled to the strength of the association: wider edges and more saturated colors represent stronger associations. The Fruchterman and Reingold [37] algorithm was used to topographically place the nodes in the network: variables with many strong connections were placed in the center of the network and variables with weaker connections are placed more at the periphery of the network [37].

The same approach was applied to estimate and visualize the concentration network of associations between the five personality traits and the seven individual Insomnia Severity Index (ISI) item scores, providing a more detailed investigation of how personality traits are associated with different aspects of

insomnia. We used polychoric correlations for the correlations involving ISI items to take the Likert-scale type variables into account.

To facilitate interpretation of the networks, we determined the "shortest paths" between all nodes. The shortest path between two nodes depends on the strength of the partial correlations between these two nodes, both directly—when present—and indirectly. The shortest path is defined as the "easiest" route through edges representing strong partial correlations [38]. As such, the shortest path between two nodes can be indirect, even when they are directly related. In addition, we determined centrality measures: strength, closeness, and betweenness [29]. The strength of a node is the sum of its absolute partial correlation coefficients. It summarizes the strength of the associations of the node with all its direct neighboring nodes. Closeness and betweenness in addition also take indirect relations of a node into account. The closeness of a node corresponds to the average "distance" between a node and all other nodes in the network [29]. The stronger the partial correlation between two nodes, the smaller their distance. Thus, the higher the closeness of a node, the stronger the average partial correlations to all other nodes. Betweenness represents the number of shortest paths that pass a node. The centrality measures give an idea of how strong the variance in a certain variable is associated with variance in the other variables. For example, if two persons have different scores on a very "central" variable, it is likely that their scores differ on most other variables as well. If these two persons have different scores on a variable that is less central, they may still have similar scores on the other variables.

2.3 RESULTS

2.3.1 *Data description*

Table 2.1 summarizes the measures of central tendency and dispersion for each of the variables. Table 2.2 provides the simple Pearson correlation coefficients among the personality traits and between each personality trait and the ISI sum score. All personality traits correlated significantly with each other, except for a lack of association of extraversion with conscientiousness, and of agreeableness with neuroticism. In agreement with previous reports, the simple Pearson correlations suggested that the ISI sum score was positively associated with neuroticism and agreeableness. In addition, unlike previous findings, openness was significantly associated with ISI sum score. In our sample, there was no significant correlation between extraversion or conscientiousness and ISI sum score.

Table 2.3 shows the polychoric correlation coefficients between the personality traits and the individual ISI items. Neuroticism, agreeableness, and openness were significantly associated with all ISI items. Extraversion and conscientiousness had significant associations with only some of the ISI items (Table 2.3),

Table 2.1: Mean (M), standard deviation (SD) and observed range for the five personality traits, the Insomnia Severity Index (ISI) sum score and the separate ISI items.

	M ± SD	Range
Personality (IPIP-mini)		
Extraversion	12.45 ± 3.66	4–20
Agreeableness	16.94 ± 2.70	4–20
Conscientiousness	14.56 ± 3.43	4–20
Neuroticism	11.25 ± 4.03	4–20
Openness	14.89 ± 3.13	5–20
Insomnia (ISI)		
ISI sum	10.61 ± 7.20	0–28
DIS	1.19 ± 1.30	0–4
DMS	1.80 ± 1.49	0–4
EMA	1.42 ± 1.37	0–4
Dissat	2.10 ± 1.25	0–4
IDF	1.60 ± 1.29	0–4
NIQoL	1.14 ± 1.09	0–4
Worry	1.36 ± 1.25	0–4

Abbreviations: DIS = Difficulty Initiating Sleep, DMS = Difficulty Maintaining Sleep, EMA = Early Morning Awakening, Dissat = Dissatisfaction with sleep, IDF = Interference with Daily Functioning, NIQoL = Noticeability of Impaired Quality of Life, Worry = Worry about sleep.

Table 2.2: Pearson correlation coefficients for the correlations among the five personality traits and between the five personality traits and the Insomnia Severity Index sum score.

	Extraversion	Agreeableness	Conscientiousness	Neuroticism	Openness
Agreeableness	**0.24**				
Conscientiousness	0.02	**0.15**			
Neuroticism	**-0.17**	0.03	**-0.15**		
Openness	**0.20**	**0.13**	**-0.11**	**-0.08**	
ISI sum	-0.04	**0.12**	-0.03	**0.38**	**-0.10**

Significant correlations are shown in **bold** font.

Table 2.3: Polychoric correlation coefficients for the correlations between each of the five personality traits and each of the individual Insomnia Severity Index items.

	Extraversion	Agreeableness	Conscientiousness	Neuroticism	Openness
DIS	0.01	**0.11**	-0.02	**0.29**	**-0.09**
DMS	-0.02	**0.14**	**0.06**	**0.28**	**-0.10**
EMA	-0.03	**0.09**	0.03	**0.25**	**-0.08**
Dissat	**-0.04**	**0.11**	-0.04	**0.36**	**-0.10**
IDF	**-0.09**	**0.11**	**-0.10**	**0.42**	**-0.06**
NIQoL	**-0.05**	**0.06**	**-0.09**	**0.34**	**-0.06**
Worry	-0.03	**0.11**	**-0.05**	**0.38**	**-0.08**

Abbreviations: DIS = Difficulty Initiating Sleep, DMS = Difficulty Maintaining Sleep, EMA = Early Morning Awakening, Dissat = Dissatisfaction with sleep, IDF = Interference with Daily Functioning, NIQoL = Noticeability of Impaired Quality of Life, Worry = Worry about sleep. Significant correlations are shown in bold font.

which corresponds to the absence of a significant association with the ISI sum score (Table 2.2).

2.3.2 *Network analysis of personality traits and ISI sum score*

Figure 2.1 shows the concentration network of partial correlations of the five personality traits and the ISI sum score. Shortest paths are shown in solid lines, the rest in dashed lines. Neuroticism and ISI showed the strongest partial correlation, even stronger than the partial correlation between any two personality traits. This indicates that neuroticism has a stronger association with insomnia severity than with any other personality trait. Conscientiousness and extraversion were only indirectly related to insomnia via neuroticism. Neuroticism, extraversion, and agreeableness scored high on the three centrality measures (Figure 2.2), and neuroticism emerged as most central in the associations among personality traits and the ISI sum score.

2.3.3 *Network analysis of personality traits and ISI items*

Figure 2.3 shows the concentration network of partial correlations of the five personality traits and each of the seven ISI items. Shortest paths are shown in solid lines, the other paths in dashed lines. Most partial correlations among ISI items were much stronger than the partial correlations between the ISI items and the personality traits. The ISI items DIS, DMS, and EMA, which represent the nocturnal complaints of insomnia, clustered together. Likewise, the daytime complaints, items IDF, NIQoL, and Worry also clustered together. The shortest paths between the nocturnal complaints to the daytime complaints were all through their common associations with dissatisfaction with sleep. Nocturnal and daytime complaints thus emerge as two smaller clusters within the net-

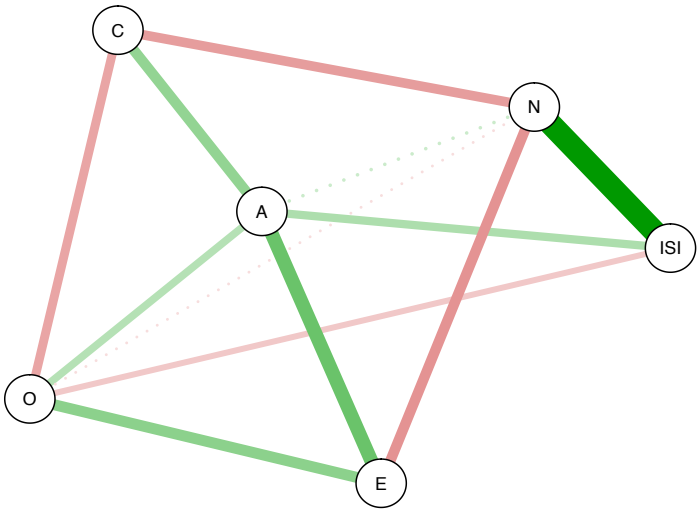

Figure 2.1: Concentration network of personality traits and the Insomnia Severity Index (ISI) sum score. Green lines indicate positive partial correlations; red lines indicate negative partial correlations. Solid lines indicate shortest paths, the other partial correlations are shown as dashed lines. The color saturation, thickness, and length of the edges represent the strength of the association. Abbreviations: A = agreeableness, C = conscientiousness, E = extraversion, N = neuroticism, O = openness. Neuroticism, agreeableness, and openness show direct relations to ISI, while conscientiousness and extraversion are indirectly related to ISI. The partial correlation between neuroticism and ISI is stronger than any of the other associations.

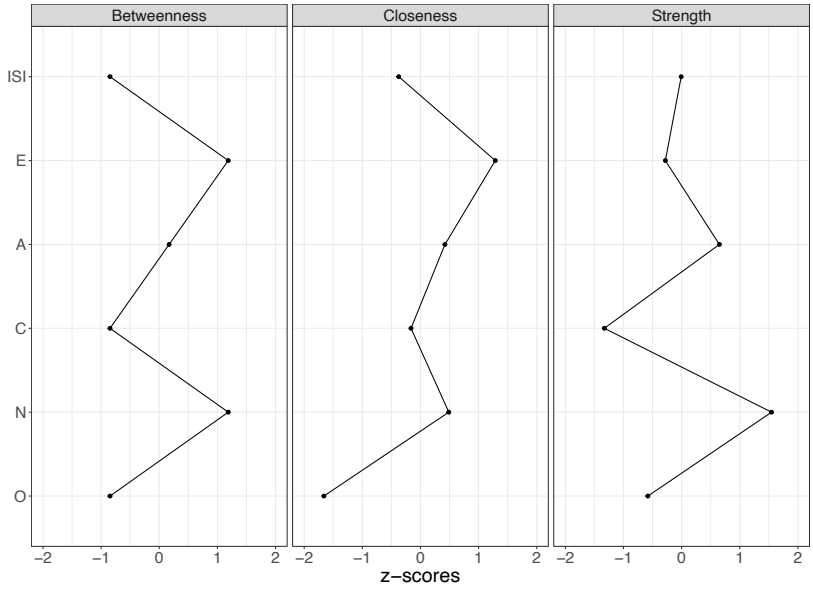

Figure 2.2: Standardized scores on the centrality measures of personality traits and the Insomnia Severity Index (ISI) sum score. Abbreviations: A = agreeableness, C = conscientiousness, E = extraversion, N = neuroticism, O = openness. The plots show that the personality traits neuroticism and extraversion are highest on all three centrality measures. Extraversion lies on the shortest path between two other nodes most often (Betweenness) and has the smallest overall distance to other nodes (Closenss), while neuroticism is connected the strongest to its direct neighbors (Strength).

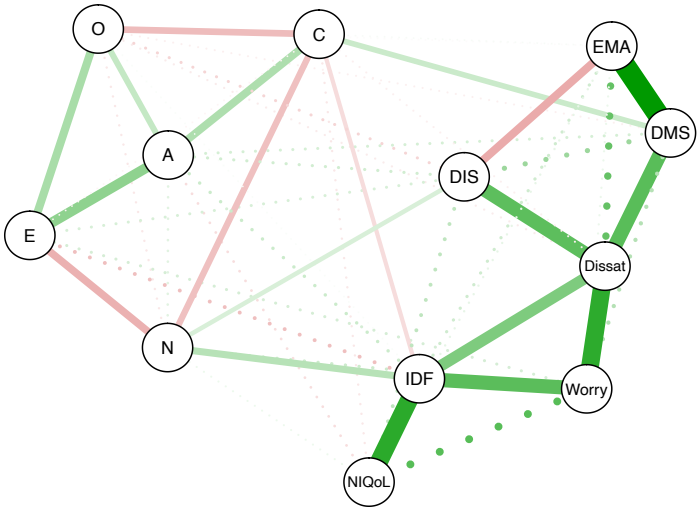

Figure 2.3: Concentration network of personality traits and the Insomnia Severity Index (ISI) items. Green lines indicate positive partial correlations; red lines indicate negative partial correlations. Solid lines indicate shortest paths, the other partial correlations are shown as dashed lines. The color saturation, thickness, and length of the edges represent the strength of the association. Abbreviations: DIS = Difficulty Initiating Sleep, Dissat = Dissatisfaction with sleep, DMS = Difficulty Maintaining Sleep, EMA = Early Morning Awakening, IDF = Interference with Daily Functioning, NIQoL = Noticeability of Impaired Quality of Life, Worry = Worry about sleep, A = agreeableness, C = conscientiousness, E = extraversion, N = neuroticism, O = openness. The graph shows two main clusters of related variables, corresponding to a personality cluster and an insomnia cluster. The insomnia cluster can be further divided into a cluster of daytime symptoms (NIQoL, IDF, and Worry) and a cluster of nocturnal symptoms (DIS, DMS, EMA) that are connected via Dissat. The shortest path that connect the personality and insomnia cluster contain neuroticism, conscientiousness, IDF, DMS, and DIS.

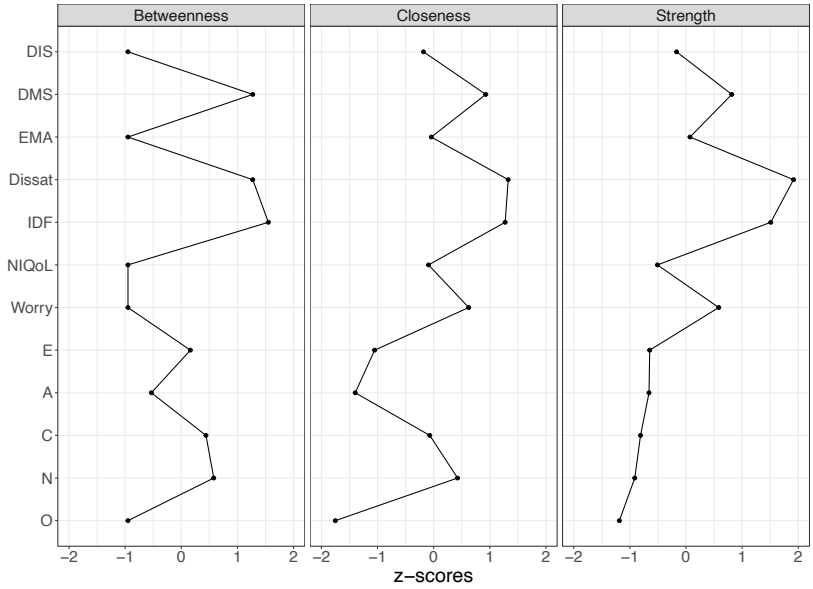

Figure 2.4: Standardized scores on the centrality measures of the personality traits and the ISI sum scores. Abbreviations: DIS = Difficulty Initiating Sleep, DMS = Difficulty Maintaining Sleep, EMA = Early Morning Awakening, Dissat = Dissatisfaction with sleep, IDF = Interference with Daily Functioning, NIQoL = Noticeability of Impaired Quality of Life, Worry = Worry about sleep, E = extraversion, A = agreeableness, C = conscientiousness, N = neuroticism, O = openness. The plots show that the ISI items Dissat and IDF are the highest on the centrality measures. IDF lies on the shortest two other nodes most often (Betweenness), while Dissat has the smallest overall distance to all other nodes (Closeness), and is connected the strongest to its direct neighbors (Strength).

work of associations, and are bridged by Dissat, suggesting that nocturnal and daytime complaints separately feed dissatisfaction. Dissatisfaction thus gets a central role in the network of nocturnal and daytime insomnia characteristics measured by the ISI (Figure 2.4). Within the cluster of nocturnal complaints, DMS and DIS are most strongly associated with parts of the network representing personality trait association: DMS with conscientiousness and DIS with neuroticism. Within the cluster of daytime complaints, IDF is most strongly associated with parts of the network representing personality trait association through its associations with, once more, conscientiousness and neuroticism. A high betweenness, closeness, and strength for ISI items IDF and DMS (Figure 2.4) suggests that individuals that are more alike with respect to these two insomnia characteristics, are also more likely to resemble each other with respect to personality traits. Since ISI items DIS, EMA, and NIQoL scored low on all three centrality measures, such matching personality is less likely for subjects that resemble each other on these insomnia characteristics.

Whereas the shortest paths of the ISI sum score with personality traits involved neuroticism, agreeableness, and openness (Figure 2.1), a different picture

emerged for the shortest paths between individual ISI items and personality traits. Neuroticism was the only trait that consistently connected the cluster of personality traits both with overall insomnia severity as well as with the cluster of individual insomnia complaints. However, the shortest paths between individual ISI items and personality traits now also included conscientiousness, rather than agreeableness and openness.

2.4 DISCUSSION

The aim of this study was to obtain an integrated view on the associations between the five factor model personality traits and insomnia, both at the level of overall insomnia severity as well as at the level of individual symptom severities. In line with previous results, the simple Pearson correlations suggested that the personality traits neuroticism and agreeableness were positively related to insomnia severity [7,8,18,20,22,25,26]. Unlike previous studies, simple Pearson correlations also suggested a negative association between openness and insomnia severity, and no significant association between conscientiousness and insomnia severity. Most personality traits showed highly significant, small to moderately sized correlations with each other. This multi-collinearity makes it difficult to discriminate direct and indirect associations of insomnia severity with the individual personality traits. Therefore, we here applied a network approach to distinguish between direct and indirect associations.

We first estimated the network of partial correlations between personality traits and the overall insomnia severity as measured with the ISI summary score. Similar to the simple correlations, insomnia severity was most strongly and directly related to neuroticism and secondarily as well to openness and agreeableness, and not directly related to extraversion and conscientiousness. In addition to the simple correlations, the network indicates possible pathways of influence that extent further than just two variables. For example, although extraversion is not directly related to insomnia, it is strongly associated to neuroticism and agreeableness, which in turn are related to insomnia. Thus, by evaluating and visualizing the associations as a network provides insight into possible pathways across multiple variables.

We subsequently estimated a network of the partial correlations between personality traits and different insomnia complaints, as measured by individual ISI items. Evaluating the item-level networks provided a number of important insights, both on the association between insomnia complaints and personality and on the associations between insomnia complaints. First, consistent with the previous analyses, neuroticism was directly related to insomnia complaints. Item-level analyses indicated that the strongest direct associations to personality concerned difficulty initiating sleep and interference with daily functioning. Interestingly, unlike the lack of a direct association of conscientiousness with overall insomnia severity, this personality trait did show direct associations specifically with the insomnia complaints of difficulty maintaining sleep and

of interference with daily functioning. Notably, while the partial correlation between conscientiousness and interference with daily functioning was negative, the partial correlation between conscientiousness and difficulty maintaining sleep was positive. This suggests that while highly conscientious people are more likely to experience difficulty maintaining sleep, they are less likely to report that sleep problems interfere with their daily functioning. The inverse associations cancel out with the use of an overall insomnia severity measure, underscoring the value of item-level analyses.

Second, the network approach revealed that daytime and nocturnal insomnia complaints seem organized in two separable clusters, that both contributed to dissatisfaction. This indicates that a summary score may dilute possible specific daytime or noctural insomnia severity. The finding could moreover have consequences for the treatment of choice for insomnia, which is cognitive behavioral therapy (CBT-I) [40]. There could be additive effects of combining interventions that address nocturnal complaints with interventions that promote coping with daytime complaints. A second possibility is that interventions that specifically promote coping with dissatisfaction could ameliorate both daytime and nocturnal complaints. Indeed, CBT-I encompasses components focusing on managing expectations and beliefs regarding sleep, improving nocturnal sleep and coping with daytime complaints [41].

The direction of influences between the insomnia complaints cannot be derived from the current cross-sectional assessment: future studies may consider repeated assessments, both during the development of insomnia as well as during intervention studies. By studying the effect of CBT-I on the individual insomnia complaints, strengths and weaknesses of the intervention could be identified and efficacy may be improved.

Both network analyses showed that neuroticism is strongly and directly related to insomnia. This is in line with previous literature [7,8,18,20,22,25,26]. Assessing neuroticism may allow for early detection of premorbid predisposition of insomnia, the first of Spielman's 3P's [5]. Coping with neuroticism has been shown feasible using both cognitive and cognitive behavioral interventions [42-44]. Moreover, knowledge about the personality traits that are characteristic of insomnia may provide clues on underlying causes of vulnerability to develop insomnia. For example, individual differences in personality traits are associated with individual differences in brain structure and brain function [12-14].

A few limitations of this study should be mentioned. First of all, participants filled out the questionnaires in an uncontrolled setting and at a self-chosen time. This resulted in a median of 7.4 months between filling out the ISI and the Mini-IPIP. However, since the Mini-IPIP assesses personality traits that are not assumed to change over time, the personality traits can be expected to be the same at the time the participants filled out the ISI. Another limitation, that has already been mentioned, is the cross-sectional set-up of this study. Whereas the current cross-sectional approach has revealed the strongest direct associations between constructs of personality and insomnia complaints, it

requires longitudinal studies to address possible changes in the associations between ISI items. We recommend longitudinal and intervention studies to not only report on ISI summary scores, but also to investigate the network of associations between items.

2.5 CONCLUSIONS

In conclusion, using network analysis in a large sample, we obtained an integrated view on the associations of personality traits with both overall insomnia severity and individual insomnia complaints. We found that examining the individual insomnia complaints provides additional information on the direct and indirect associations both between personality traits and insomnia, as well as between the different insomnia complaints. The approach allowed us to discriminate direct associations from indirect relations and thereby identified possible targets for improving CBT-I with the highest probability of effectively changing the network of associated complaints.

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3

INSOMNIA SUBTYPES

ORIGINAL ARTICLE

SUMMARY

BACKGROUND Insomnia disorder is the second most prevalent mental disorder, and it is a primary risk factor for depression. Inconsistent clinical and biomarker findings in patients with insomnia disorder suggest that heterogeneity exists and that subtypes of this disease remain unrecognised. Previous top-down proposed subtypes in nosologies have had insufficient validity. In this large-scale study, we aimed to reveal robust subtypes of insomnia disorder by use of data-driven analyses on a multidimensional set of biologically based traits.

METHODS In this series of studies, we recruited participants from the Netherlands Sleep Registry, a database of volunteers aged 18 years or older, who we followed up online to survey traits, sleep, life events, and health history with 34 selected questionnaires of which participants completed at least one. We identified insomnia disorder subtypes by use of latent class analyses. We evaluated the value of our identified subtypes of insomnia disorder by use of a second, non-overlapping cohort who were recruited through a newsletter that was emailed to a new sample of Netherlands Sleep Registry participants, and by assessment of within-subject stability over several years of follow-up. We extensively tested the clinical validity of these subtypes for the development of sleep complaints, comorbidities (including depression), and response to benzodiazepines; in two subtypes of insomnia disorder, we also assessed the clinical relevance of these subtypes by use of an electroencephalogram biomarker and the effectiveness of cognitive behavioural therapy. To facilitate implementation, we subsequently constructed a concise subtype questionnaire and we validated this questionnaire in the second, non-overlapping cohort.

FINDINGS 4322 Netherlands Sleep Registry participants completed at least one of the selected questionnaires, a demographic questionnaire, and an assessment of their Insomnia Severity Index (ISI) between March 2, 2010, and Oct 28, 2016. 2224 (51%) participants had probable insomnia disorder, defined as

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an ISI score of at least 10, and 2098 (49%) participants with a lower ISI score served as a control group. With a latent class analysis of the questionnaire responses of 2224 participants, we identified five novel insomnia disorder subtypes: highly distressed, moderately distressed but reward sensitive (i.e., with intact responses to pleasurable emotions), moderately distressed and reward insensitive, slightly distressed with high reactivity (to their environment and life events), and slightly distressed with low reactivity. In a second, non-overlapping replication sample of 251 new participants who were assessed between June 12, 2017, and Nov 26, 2017, five subtypes were also identified to be optimal. In both the development sample and replication sample, each participant was classified as having only one subtype with high posterior probability (0·91–1·00). In 215 of the original sample of 2224 participants with insomnia who were reassessed 4·8 (SD 1·6) years later (between April 13, 2017, and June 21, 2017), the probability of maintaining their original subtype was 0·87, indicating a high stability of the classification. We found differences between the identified subtypes in developmental trajectories, response to treatment, the presence of an electroencephalogram biomarker, and the risk of depression that was up to five times different between groups, which indicated a clinical relevance of these subtypes.

INTERPRETATION High-dimensional data-driven subtyping of people with insomnia has addressed an unmet need to reduce the heterogeneity of insomnia disorder. Subtyping facilitates identification of the underlying causes of insomnia, development of personalised treatments, and selection of patients with the highest risk of depression for inclusion in trials regarding prevention of depression.

3.1 INTRODUCTION

Insomnia is a common health problem; a third of the population report sleep complaints and about 10% of the population meet the diagnostic criteria for insomnia disorder [1,2], making it the second most prevalent mental disorder [3]. Despite the high prevalence and considerable heritability of insomnia [4] and the identification of genes that confer an associated risk of insomnia [5,6], it has been difficult to characterise insomnia consistently with respect to cognition [7], mood [8], family history [9], history of life events [10], personality [11], polysomnography [12], sleep microstructure [13], and brain imaging [14]. Such inconsistencies suggest unrecognised subtypes of insomnia disorder and stall progress in our understanding of its underlying mechanisms, with which we could improve interventions. Subtypes of insomnia disorder that were previously proposed top down [15–18] predominantly focused on sleeprelated characteristics (such as sleeponset insomnia), had low reliability [15,16], and were discarded from major nosologies [17,18].

However, we suspected that clearer subtypes of insomnia disorder might emerge if they were developed bottom-up and data-driven, with a multidimensional set of stable, biologically based non-sleep characteristics that are relevant to insomnia [19]. Such a wider perspective on discriminating characteristics has been shown to be important in other disorders. For example, subtyping attention deficit hyperactivity disorder according to temperament trait dimensions explained more of its heterogeneity than previous nosological criteria [20]. It is conceivable that insomnia disorder could similarly represent a heterogeneous group of patients in whom different underlying mechanisms are reflected in biologically based traits that lead to indistinguishable sleep complaints. Finding insomnia disorder subtypes would then require inclusion of traits that might only indirectly relate to sleep but can be highly relevant to insomnia, such as hyperarousal, personality, and mood traits [5,6,19].

The biological basis of traits related to insomnia (supplementary tables A.1 – A.3) [19] makes it conceivable that several specific combinations of traits can be unfavourable for sleep regulation. Our previous genome-wide association studies [5,6] indicated that insomnia disorder is genetically more closely related to attributes associated with mood, personality, and wellbeing than to sleep-related phenotypes. We therefore aimed to investigate whether insomnia disorder presents as different subtypes that are reflected in a multivariate pattern of stable characteristics, such as life history, trait positive and negative affect, and personality.

Research in context

evidence before this study

Clinical and biomarker findings on insomnia disorder show inconsistencies across patients and studies, and this heterogeneity is suggested to be caused by unrecognised subtypes. Subtypes of insomnia disorder have previously been proposed top-down. It was presumed that these subtypes would differ with respect to stable sleep-related characteristics. Unfortunately, such subtypes had insufficient reliability and validity, so heterogeneity still prevails. No previous study investigated whether subtypes can be revealed using a high-dimensional data-driven approach, including biologically based traits that could more indirectly be related to insomnia. We searched PubMed for work published before Feb 19, 2018, with the search terms "insomnia AND data-driven AND subtype", which revealed only two papers. One of these papers was a study report that included insomnia as a dimension to subtype 203 patients with major depressive disorder. The other paper was our theoretical systematic review on variables of relevance in a high-dimensional data-driven approach to find subtypes of insomnia.

ADDED VALUE OF THIS STUDY

To our knowledge, our study represents the first identification of five novel and robust subtypes of insomnia disorder and the first demonstration of the usefulness of these subtypes in reducing clinical and biomarker heterogeneity. We used a high-dimensional data-driven analysis of 34 biologically based traits that were assessed by questionnaires in a large sample (4322 participants) among which 2224 participants had probable insomnia disorder. We also developed and validated a more concise Insomnia Type Questionnaire with the most discriminating 200 of the original 523 questions, representing 17 of the original 26 characteristics, to reliably assess subtypes in an independent sample. After a follow up of 4·8 (range 0·5–7·0) years, there was a probability of 0·87 that participants would maintain their original subtype, which was in sharp contrast to the low stability of previous subtypes that were suggested in top-down studies (e.g., a third of participants maintained their subtype for 4 months). In derived and independent samples, we validated the clinical relevance of our identified subtypes by identification of subtype differences in developmental trajectories of sleep complaints, health risks, response to pharmacological and non-pharmacological treatments, and a neurophysiological biomarker.

IMPLICATIONS OF ALL AVAILABLE EVIDENCE

Marked subtype differences in the risk of depression in people with insomnia could enable selection of high-risk individuals for preventive interventions by use of the Insomnia Type Questionnaire that we developed, which includes automated scoring. By reducing previously unrecognised heterogeneity, subtyping will facilitate identification of biomarkers, elucidation of the mechanisms of insomnia, and development of personalised treatments for insomnia disorder. Subtyping is reliable and can be accomplished in large populations by use of the internet.

3.2 METHODS

3.2.1 *Study design and participants*

We used data provided by participants from the Netherlands Sleep Registry (NSR), an online platform and linked database that extensively surveys sleep, personality and affect traits, life events, and health conditions [19]. NSR volun-

teers are recruited via media, advertisements, and flyers that are distributed at healthcare institutions and conventions. Recruitment communications for the NSR stress the need for volunteers who cover the spectrum of those who sleep well to those who sleep poorly. As a result, participants in the NSR database represent a uniform distribution with respect to the severity of insomnia: 38% of participants have insomnia, 29% of participants have subclinical insomnia, and 33% of participants have clinical insomnia [21]. The only inclusion criterion was an age of 18 years or older. Participants completed a variable number of randomly selected questionnaires (of 34 questionnaires) at their convenience, resulting in a varying number and set of completed questionnaires between participants. Those with an insomnia severity index (ISI) score of at least 10 were included as cases with probable insomnia disorder; participants with an ISI score of less than 10 were included as controls. Among the participants with probable insomnia disorder, we invited a randomly drawn subset by email to participate in a longitudinal follow up. Additionally, new NSR participants were recruited by newsletter for validation in a second, nonoverlapping cohort. The Medical Ethical Committee of the Academic Medical Centre of Amsterdam and the Central Committee on Research Involving Human Subjects approved of implicit informed consent.

3.2.2 *Model development*

Characteristics that were relevant to insomnia were first identified by a systematic review [19] and an assessment of genetic correlations [5,6]. Sufficient data were available for 34 characteristics, each representing a questionnaire sum score, that covered features of life history, fatigue and arousal, personality, mood, and happiness, among others (supplementary table A.4). To prevent multicollinearity, we selected only the characteristics that had the lowest median correlation with each of the other characteristics, preserving 26 characteristics for analyses. The preserved characteristics and observed score ranges are shown in the supplementary table A.5.

To identify subtypes among the patients with insomnia disorder, we chose a modelbased unsupervised clustering technique—latent class analysis—because this approach can handle missing data, include variables that are measured on different scales, and classify new patients (supplementary section A.1.1). To determine the most probable number of subtypes, we increased the number of classes stepwise, and we selected the model that minimised the Bayesian information criterion. Any participant who completed even only one characteristic questionnaire is of value to estimate the latent class model, because even one observation carries information on the observed range of that characteristic. However, a profile of several characteristics is required to subtype an individual, and the availability of only a few characteristics is insufficient to identify the subtype profile to which an individual belongs. Therefore, we evaluated the quality of the model on a subsample of 1046 individuals who completed at

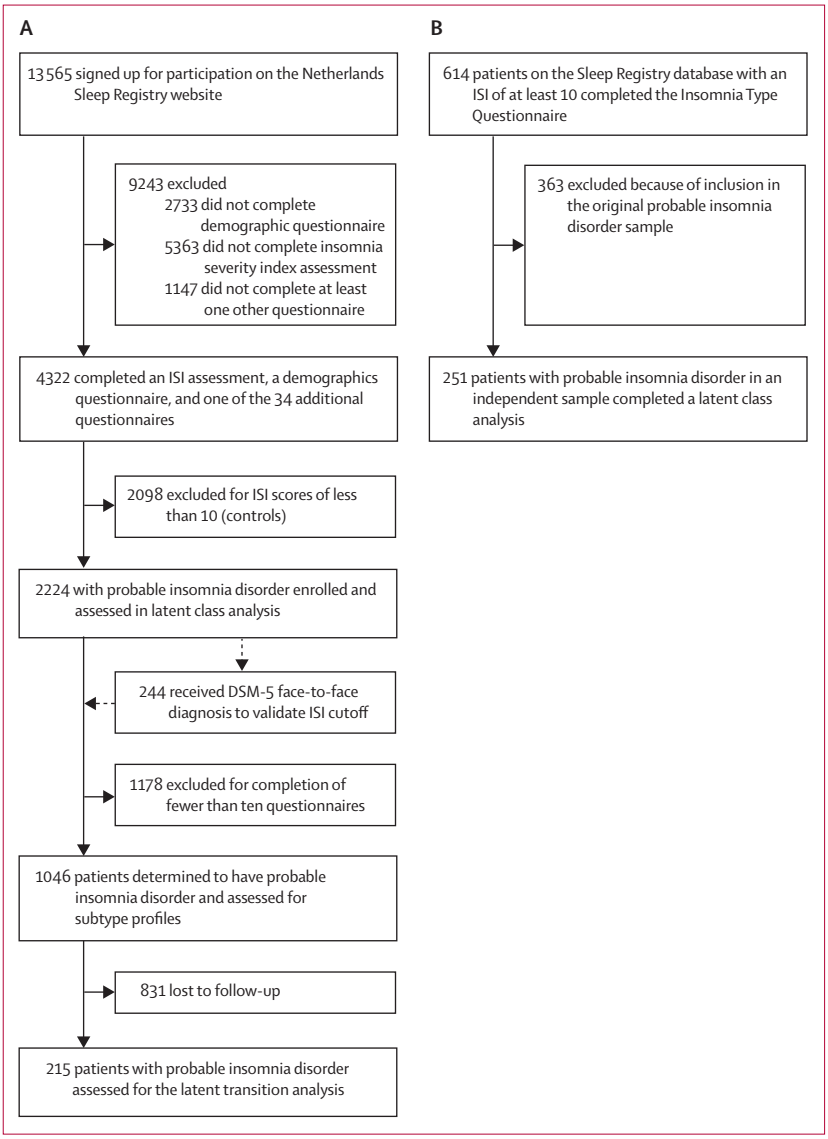

Figure 3.1: Trial profile of the main cohort (A) and of a non-overlapping cohort used to validate the subtypes (B).

least ten and up to 26 questionnaires, each representing independent characteristics (supplementary figure A.2). Details on model estimation, evaluation, and assumptions are shown in the supplement (section A.1.1).

For multivariate visualisation of subtypes, we standardised each individual characteristic score to the corresponding distribution of scores in the control group. The values of positive characteristics (such as wellbeing) were reverse coded and renamed (e.g., reduced wellbeing), such that higher values would uniformly indicate higher general distress. To quantify the effect sizes of group differences, we computed Cohen's d, often labelled small (0·2), medium (0·5), and large (0·8) [22].

To facilitate implementation, we used a regression with least absolute shrinkage and selection (lasso) regularisation to select a subset of characteristics that still accurately predicted class membership, from which we developed the Insomnia Type Questionnaire (ITQ; see supplementary section A.1.2).

3.2.3 *Model validation*

We recruited a new, non-overlapping validation sample of people with probable insomnia disorder (with an ISI score of at least 10 [21]) through the NSR. With this sample, we validated the robustness of the number of classes by use of a latent class analysis and again selected the model that minimised the Bayesian information criterion. Moreover, we verified the use of the ITQ in subdividing these patients into subtypes. Details on regularisation and ITQ construction are shown in the supplementary section A.1.2.

Finally, to validate the traitlike stability of subtype classification, we assessed the consistency of subtype membership over a maximum of 7 years by use of a latent transition analysis (supplementary section A.1.3) in a proportion of the original participants.

3.2.4 *Clinical validation*

After the subtypes of insomnia disorder were found and validated, we extensively investigated clinical relevance of these subtypes for the developmental trajectories of sleep complaints, current comorbidities, risk of depression, and response to benzodiazepine intake. We also investigated the clinical relevance of two subtypes for an electroencephalogram biomarker and the effectiveness of cognitive behavioural therapy (CBT) for insomnia (supplementary figure A.3).

To assess clinical relevance in NSR participants, we first used χ^2 tests to evaluate differences in the developmental trajectories of sleep complaints across the lifespan between the subtypes, and we used Fisher's exact tests for differences in comorbid sleepdisorders, lifetime and current risk of depression, and other comorbidities.

Second, a subsample of NSR participants with insomnia disorder used five-point bipolar Likerttype scales to rate whether difficulty initiating sleep, diffi-

culty maintaining sleep, early morning awakening, and fatigue were worsened or improved after incidental benzodiazepine use the preceding night, relative to their usual severity. Ratings by subtype were compared with F tests and t tests.

Third, in a separate sample, we investigated the subtype dependent effects of 4 weeks of online CBT for insomnia on the ISI score of people diagnosed with insomnia disorder [17,18]. ITQ-based subtyping identified sufficient participants of subtype 2 and subtype 4. We used mixed effect models to compare treatment effects in this sample.

Finally, as a preliminary illustration of the potential of subtyping in finding clinically relevant biomarkers and clues to differential underlying brain mechanisms, we subtyped volunteers of an independent study on electroencephalogram eventrelated potentials (ERPs). Among participating patients diagnosed with insomnia disorder [17,18], only those with insomnia disorder subtypes 2 and 4 were sufficiently represented (defined as more than ten participants per group) for reliable ERP averages. The ERP results of these participants were compared with those of controls without sleep complaints. In a so-called auditory oddball task, volunteers listen to repeated standard tones and occasional tones of a deviating pitch. Electroencephalograms are simultaneously recorded, which allows for an evaluation of trait-like brain responses that reflect information-processing aspects such as adaptation and attention. Artifact-free ERPs at the Pz location of the 10-20 system of electrodes that were referenced to both mastoids were averaged over 170 standard tones and 30 deviating tones. We used cluster-based random permutation tests to evaluate the significance of group differences across the ERP curve, covering early sensory responses, a midlatency indicator of adaptation, attention, and salience (determined by the P300 potential amplitude), and a late indicator of emotional relevance (determined by the late positive potential amplitude) [23].

3.2.5 *Statistical analysis*

Latent class analysis and latent transition analysis were done with Latent GOLD version 5.0. Other analyses used the R (version 3.2.4) packages effsize, leaps, glmnet, and stabs, SPSS (version 23.0), and MLwiN version 2.02. The analysis scheme and corresponding subsamples are shown in the supplementary figures A.2 and A.3.

3.3 RESULTS

All questionnaires (supplementary table A.4) were completed online between March 2, 2010, and Nov 26, 2017. Face-to-face interviews in a subsample of 244 participants were conducted between Jan 9, 2012, and Sept 30, 2016, at the Netherlands Institute for Neuroscience (Amsterdam, The Netherlands). Data collected between March 2, 2010, and Oct 28, 2016, in participants of the Netherlands Sleep Registry (NSR) were used (figure 3.1). Of the 13565 people

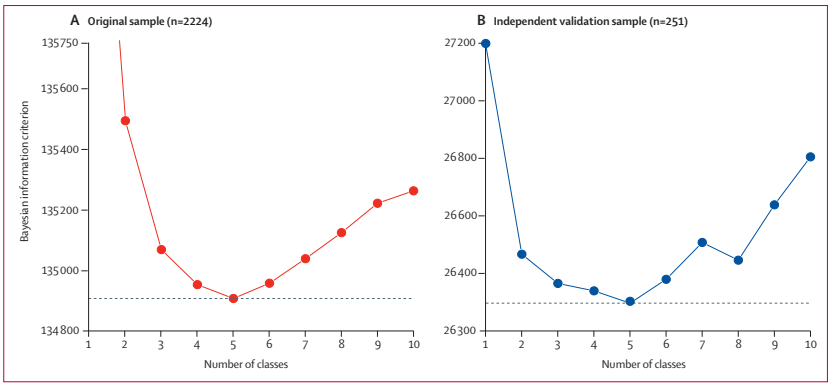

Figure 3.2: Goodness of fit of the BIC. BIC for 1–10 latent class models in the original sample (A) and the independent validation sample (B). The BIC indicates the goodness of fit of a model and penalises model complexity. For models within a given sample, lower BIC values indicate better fit. In both samples, the BIC is minimised at five classes. BIC = Bayesian information criterion.

who signed up for the NSR, 4322 participants completed at least one of the 34 included questionnaires, in addition to a demographics questionnaire and an assessment of their ISI. 2224 (51%) participants fulfilled the criterion of an ISI score of at least 10 for probable insomnia disorder in community samples [21] and were included in the latent class analysis. 2098 (49%) participants had an ISI score of less than 10 and served as controls. The validity of the ISI cut-off was confirmed in a subsample of 244 (11%) of the participants, who were also diagnosed in a face-to-face interview with DSM-5 criteria [17]. 195 (80%) of these participants were diagnosed with insomnia disorder with these criteria, of whom 185 (76%) had an ISI of at least 10 (sensitivity 94·9%); of the 49 (20%) participants without this diagnosis, 41 (17%) had an ISI of less than 10 (specificity 83·7%). In absence of face-to-face diagnosis of the other participants, our definition of insomnia disorder, for brevity, should be read as probable insomnia disorder, as suggested by the severity of insomnia symptoms. On April 13, 2017, a newsletter was sent among registered NSR users who opted-in for communications, to collect follow-up data, which were collected between April 13, 2017, and June 21, 2017. Of the 1046 participants who were originally assessed for at least ten characteristics (i.e., with at least ten questionnaires), 831 (79%) participants were lost to follow-up and 215 (21%) participants were assessed in the follow-up latent transition analysis.

The 2224 participants with probable insomnia disorder had a mean age of 51·1 (SD 13·7) years and 1726 (78%) participants with probable insomnia disorder were female (table 3.1). 2098 control participants (with an ISI$<$10) had a mean age of 47·2 (15·8) years, and 1558 (74%) control participants were female.

With a minimal Bayesian information criterion, we found that a five-class model was optimal among the 2224 participants whose responses were used to estimate the model. To interpret the estimated model, we used this model

to subtype the 1046 (47%) participants who completed at least ten and up to 26 questionnaires (figure 3.2A; supplementary table A.6). Most participants were uniquely assigned to only one of the five subtypes, as indicated by high posterior probabilities (0·91–0·99) and a low misclassification estimate (13%; supplementary table A.7). The demographics, insomnia characteristics, and comorbidities of the 1046 people with insomnia who completed at least ten questionnaires are shown in table 3.1.

Their multivariate profiles of the group means of characteristics (life history and affect and personality traits) for each subtype, ranked clockwise according to subtype-explained variance (from 41% variance in negative affect to 15% variance in behavioural activation), are shown in figure 3.3, and all 26 characteristics are shown in the supplementary figure A.4. The diameter of the profiles represents the overall level of burdensome characteristics–i.e., high for one subtype, moderate for two subtypes, and slight for two subtypes. The profiles also discriminate between subtypes by their multivariate fingerprint shape.

Among the 1046 people with insomnia who completed at least ten questionnaires, 200 (19%) participants were classified in subtype 1, which indicated high general distress (figure 3.3A). The three characteristics that deviated most markedly from control group participants concerned high pre-sleep arousal (Cohen's d=2·55) and negative affect (d=2·31) and reduced subjective happiness (d=2·15; p<0·0001 for all three). Most other characteristics differed by more than 1 standard deviation, except for reduced positive rumination (d=0·41; p<0·0001) and reduced experience of pleasure (d=0·31; p=0·0016), which were within 0·5 standard deviations of the control group results. Subtype 1 can be termed highly distressed insomnia disorder.

323 (31%) participants were classified in subtype 2 and 153 (15%) participants were classified in subtype 3; both showed moderate general distress but could be distinguished by their profile (figure 3.3B). For subtype 2, pre-sleep arousal (d=1·57), insomnia response to stress (d=1·38), and negative affect (d=1·12) deviated most markedly from control participants (p<0·0001 for all three). Relative to the overall moderate general distress, the high arousal and response to stress of subtype 2 appears like the disorder that is conventionally referred to as psychophysiological insomnia. Subtype 2 participants did not show particularly low positive affect (d=0·06;p=0·3), positive rumination (d=–0·13; p=0·06), or experience of pleasure (d=–0·36; p<0·0001); all of these findings were within 0·5 standard deviations of the results of control participants, and even appeared more favourable regarding positive rumination and experience of pleasure. Subtype 2 can be termed moderately distressed, reward-sensitive insomnia disorder.

By contrast, subtype 3 is primarily characterised by reduced positivity. Specifically, reduced subjective happiness (d=1·89), positive affect (d=1·34), positive rumination (d=1·18), and experience of pleasure (d=1·00) all deviated from the findings in control participants by more than 1 standard deviation (p<0·0001 for all four). Positive rumination and experience of pleasure were more reduced in subtype 3 than in any other subtype. Subtype 3 also differed markedly from

Table 3.1: Demographics, insomnia characteristics, and sample prevalence estimates of current sleep disorders, main ICD-10 disorder categories, the ICD-10 mental disorder subcategories, as well as lifetime depression, for controls and each of the insomnia disorder subtypes.

	Control	Insomnia disorder subtype (n=1046)				
		1 (highly distressed)	2 (moderately distressed, reward sensitive)	3 (moderately distressed, reward insensitive)	4 (slightly distressed, high reactive)	5 (slightly distressed, low reactive)
Demographics						
Number (% with subtype)	2098	200 (19%)	323 (31%)	153 (15%)	209 (20%)	161 (15%)
Number of women (% with subtype)	1558	164 (20%)	271 (33%)	100 (12%)	176 (22%)	106 (13%)
Number of men (% with subtype)	540	36 (16%)	52 (23%)	53 (23%)	33 (14%)	55 (24%)
Age, years	47·2 (15·8)*†‡	49·5 (12·5)†‡	48·9 (14·3)*†‡	53·9 (13·9)§	54·0 (12·1)§¶	56·6 (12·5)§¶
Insomnia characteristics						
Insomnia severity index score	4·0 (2·9)*†‡§¶	17·8 (4·9)*†‡§	15·8 (4·1)¶	16·5 (4·6)‡¶	15·0 (3·9)¶	14·8 (3·7)*¶
Difficulty initiating sleep, mean score	0·5 (0·6)*†‡§¶	2·0 (1·4)	1·8 (1·3)	1·9 (1·4)	1·6 (1·4)	1·7 (1·3)
Difficulty maintaining sleep, mean score	0·6 (0·8)*†‡§¶	2·8 (1·3)	2·6 (1·2)	2·8 (1·3)	2·8 (1·3)	2·7 (1·2)
Early morning awakening, mean score	0·5 (0·7)*†‡§¶	2·3 (1·4)	2·1 (1·3)	2·1 (1·4)	2·1 (1·3)	2·1 (1·3)
Dissatisfied with sleep, mean score	1·0 (0·8)*†‡§¶	3·1 (0·8)	3·0 (0·8)	3·0 (0·7)	2·9 (0·8)	2·9 (0·7)
Interference with daily functioning, mean score	0·6 (0·7)*†‡§¶	2·9 (0·9) *†‡§	2·4 (0·9)‡¶	2·6 (1·0)†‡¶	2·2 (1·1)*¶	2·0 (1·0)*§¶
Noticeable impaired quality of life, mean score	0·5 (0·7)*†‡§¶	2·1(1·0)*†‡§	1·7 (0·9)¶	1·8 (1·1)‡¶	1·6 (1·0)¶	1·5 (0·9)*¶
Worried about sleep, mean score	0·3 (0·6)*†‡§¶	2·5 (1·0)†‡§	2·2 (0·9)†‡¶	2·3 (1·0)†‡	1·8 (1·0)*§¶	1·8 (0·9)*§¶
Sleep duration	7 h 24 min (59 min) *†‡§¶	6 h 8 min (1 h 57 min)	6h 7 min (1 h 19 min)	5 h 58 min (1 h 34 min)	5 h 47 min (1 h 23 min)	5 h 51 min (1 h 16 min)
Co-occurring sleep disorders						
Restless leg syndrome	94 (7·1%)*†§¶	32 (19·8%)	51 (19·1%)	22 (16·4%)	32 (17·4%)	14 (10·8%)
Periodic leg movement disorder	13 (1·0%)†§¶	15 (9·3%)	11 (4·1%)	4 (3·0%)	10 (5·4%)	3 (2·3%)
Obstructive sleep apnoea syndrome	128 (9·6%)*†§¶	39 (24·1%)	54 (20·2%)	32 (23·9%)	33 (17·9%)	19 (14·6%)
Narcolepsy	1 (0·1%)	2 (1·2%)	0	0	2 (1·1%)	0
Parasomnia						
Recurrent nightmares	67 (5·0%)*†§¶	42 (25·9%)*†‡§	43 (16·1%)†‡¶	17 (12·7%)¶	12 (6·5%)§¶	8 (6·2%)§¶
Night terror	7 (0·5%)	3 (1·9%)	2 (0·7%)	3 (2·2%)	1 (0·5%)	0
Sleepwalking	2 (0·2%)	1 (0·6%)	0	1 (0·7%)	1 (0·5%)	0
Sleep-related hallucinations	25 (1·9%)¶	16 (9·9%)	10 (3·7%)	3 (2·2%)	5 (2·7%)	3 (2·3%)
Sleep-related dissociative episodes	1 (0·1%)	2 (1·2%)	1 (0·4%)	0	1 (0·5%)	0
Eating or drinking during sleep	0¶	3 (1·9%)	1 (0·4%)	2 (1·5%)	2 (1·1%)	0
Confusional arousals	16 (1·2%)†§¶	30 (18·5%)*†‡§	13 (4·9%)‡¶	2 (1·5%)¶	7 (3·8%)¶	0§¶
Sleep-related leg cramps	96 (7·2%)¶	25 (15·4%)	26 (9·7%)	17 (12·7%)	23 (12·5%)	13 (10·0%)
Sleep paralysis	18 (1·4%)	7 (4·3%)	8 (3·0%)	5 (3·7%)	5 (2·7%)	2 (1·5%)
Rapid eye movement phase sleep behaviour	7 (0·5%)	6 (3·7%)	3 (1·1%)	3 (2·2%)	0	1 (0·8%)
Sleep-related bruxism	68 (5·1%)	12 (7·4%)	24 (9·0%)	6 (4·5%)	8 (4·3%)	8 (6·2%)
Sleep-related groaning or catathrenia	158 (11·9%)§¶	43 (26·5%)	53 (19·9%)	24 (17·9%)	28 (15·2%)	11 (8·5%)
Exploding head syndrome	35 (2·6%)†§¶	17 (10·5%)	16 (6·0%)	6 (4·5%)	13 (7·1%)	8 (6·2%)
Sleep related enuresis	1 (0·1%)	0	0	0	0	0

(Table 1 continues on next page)

Table 3.1: (continued)

	Control	Insomnia disorder subtype (n=1046)				
		1 (highly distressed)	2 (moderately distressed, reward sensitive)	3 (moderately distressed, reward insensitive)	4 (slightly distressed, high reactive)	5 (slightly distressed, low reactive)
(Continued from previous page)						
Comorbidities in main ICD-10 disease categories						
Infectious	11 (0·8%)	5 (3·1%)	2 (0·7%)	0	7 (3·8%)	1 (0·8%)
Neoplasms	13 (1·0%)§	3 (1·9%)	14 (5·2%)	3 (2·2%)	2 (1·1%)	3 (2·3%)
Blood-related	11 (0·8%)	4 (2·5%)	3 (1·1%)	5 (3·7%)	6 (3·3%)	1 (0·8%)
Endocrine	71 (5·3%)*†§¶	30 (18·5%)	36 (13·5%)	18 (13·4%)	26 (14·1%)	10 (7·7%)
Nervous system	14 (1·1%)†‡	4 (2·5%)	0*†‡	4 (3·0%)§	8 (4·3%)§	6 (4·6%)§
Eye	172 (12·9%)	25 (15·4%)	46 (17·2%)	25 (18·7%)	24 (13·0%)	17 (13·1%)
Ear	85 (6·4%)	18 (11·1%)	25 (9·4%)	11 (8·2%)	19 (10·3%)	11 (8·5%)
Circulatory system	64 (4·8%)§¶	20 (12·3%)	26 (9·7%)	11 (8·2%)	13 (7·1%)	11 (8·5%)
Respiratory system	81 (6·1%)	8 (4·9%)	22 (8·2%)	16 (11·9%)	20 (10·9%)	17 (13·1%)
Digestive system	29 (2·2%)§¶	14 (8·6%)	17 (6·4%)	8 (6·0%)	5 (2·7%)	3 (2·3%)
Skin	114 (8·6%)	25 (15·4%)	36 (13·5%)	21 (15·7%)	23 (12·5%)	13 (10·0%)
Musculoskeletal system	177 (13·3%)*†§¶	47 (29·0%)	67 (25·1%)	30 (22·4%)	41 (22·3%)	26 (20·0%)
Genitourinary system	71 (5·3%)*†§¶	20 (12·3%)	32 (12·0%)	19 (14·2%)	22 (12·0%)	11 (8·5%)
Pregnancy	5 (0·4%)	1 (0·6%)	1 (0·4%)	1 (0·7%)	0	0
Perinatal originating conditions	2 (0·2%)	1 (0·6%)	1 (0·4%)	1 (0·7%)	0	0
Congenital malformations	6 (0·5%)	2 (1·2%)	5 (1·9%)	0	1 (0·5%)	0
Symptoms not elsewhere classified	83 (6·2%)*†§¶	49 (30·2%)‡§	51 (19·1%)‡¶	33 (24·6%)‡	38 (20·7%)‡	12 (9·2%)*†§¶
Consequences of external causes	123 (9·2%)*†§¶	36 (22·2%)	46 (17·2%)	32 (23·9%)	34 (18·5%)	17 (13·1%)
Comorbidities in ICD-10 subcategories of mental and behavioural disorders (categories F00–F99, except F70–F79)						
Organic	5 (0·4%)	3 (1·9%)	3 (1·1%)	1 (0·7%)	0	0
Substance-related	1 (0·1%)*¶	3 (1·9%)	3 (1·1%)	4 (3·0%)	0	0
Schizophrenia	3 (0·2%)	3 (1·9%)	0	0	1 (0·5%)	0
Mood	38 (2·9%)*§¶	59 (36·4%)*†‡§	16 (6·0%)*†¶	25 (18·7%)†‡§¶	1 (0·5%)*§¶	3 (2·3%)*¶
Anxiety	39 (2·9%)*§¶	59 (36·4%)*†‡§	33 (12·4%)†‡¶	14 (10·4%)†‡¶	6 (3·3%)*§¶	1 (0·8%)*§¶
Physiological or physical	0*†§¶	10 (6·2%)	7 (2·6%)	4 (3·0%)	3 (1·6%)	0
Personality	7 (0·5%)*§¶	26 (16·0%)*†‡§	6 (2·2%)¶	6 (4·5%)¶	1 (0·5%)¶	0¶
Developmental	2 (0·2%)	1 (0·6%)	3 (1·1%)	1 (0·7%)	0	0
Childhood onset	6 (0·5%)§¶	17 (10·5%)*†‡§	11 (4·1%)‡¶	3 (2·2%)¶	2 (1·1%)¶	0§¶
Lifetime depression, anxiety, and bipolar disorder						
Lifetime depression	155 (11·6%)*§¶	88 (54·3%)*†‡§	72 (27·0%)†‡¶	46 (34·3%)†‡¶	15 (8·2%)*§¶	17 (13·1%)*§¶
Lifetime anxiety	69 (5·2%)*‡§¶	60 (37·0%)*†‡§	47 (17·6%)†‡¶	20 (14·9%)†‡¶	12 (6·5%)*§¶	1 (0·8%)*§¶
Lifetime bipolar	10 (0·8%)¶	8 (4·9%)*‡§	2 (0·7%)¶	0¶	2 (1·1%)	0¶

Data are n (%) or mean (SD). Data about sleep disorders and other comorbidities are from 1333 participants in the control group, 162 participants with insomnia disorder subtype 1, 267 participants with insomnia disorder subtype 2, 134 participants with insomnia disorder subtype 3, 184 participants with insomnia disorder subtype 4, and 130 participants with insomnia disorder subtype 5 who completed online structured interview modules. Sleep duration was obtained from the Pittsburgh Quality of Sleep Index. Description of the ICD-10 disease categories is available online Restless leg syndrome was with the four diagnostic criteria defined by the International Restless Leg Syndrome Study Group. Estimates of periodic leg movement disorder, obstructive sleep apnoea syndrome, and narcolepsy were made without the polysomnographic assessment required for diagnosis. Obstructive sleep apnoea syndrome was assessed with the Berlin Questionnaire. *p<0·05 versus insomnia disorder subtype 3 after Bonferroni correction. †p<0·05 versus insomnia disorder subtype 4 after Bonferroni correction. ‡p<0·05 versus insomnia disorder subtype 5 after Bonferroni correction. §p<0·05 versus insomnia disorder subtype 2 after Bonferroni correction. ¶p<0·05 versus insomnia disorder subtype 1 after Bonferroni correction.

Table 1: **Demographics, insomnia characteristics, and sample prevalence estimates of current sleep disorders, main ICD-10 disorder categories, the ICD-10 mental disorder subcategories, as well as lifetime depression, for controls and each of the insomnia disorder subtypes**

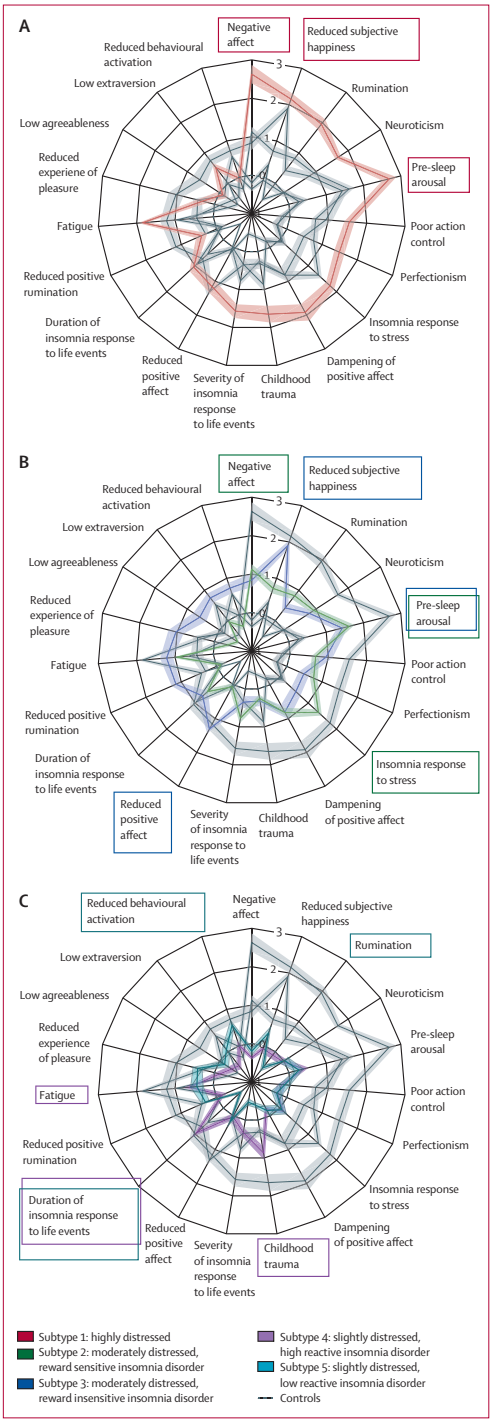

Figure 3.3: Multivariate profile plots of the subtypes of insomnia. Data are scaled subtype group means (95% CIs), in which Z scores have been standardised to the mean and standard deviation of controls for each characteristic, with the subtype-explained variance, ranked clockwise from the top. (A) Highly distressed subtype (subtype 1). (B) Moderately distressed subtypes (subtype 2, which was reward sensitive, and subtype 3, which was reward insensitive). (C) Low distress subtypes (subtype 4, which was high reactive, and subtype 5, which was low reactive). Positive characteristics (e.g., positive rumination), were reverse-coded and renamed (e.g., reduced positive rumination), such that higher valued uniformly indicate higher general distress for all characteristics throughout the plot. Coloured boxed indicate the three characteristics that differentiate each subtype most from control participants.

controls (d=1·42; p<0·0001), but not from subtype 2 (d=0·17; p=0·12), regarding pre-sleep arousal. Subtype 3 can be termed moderately distressed, reward-insensitive insomnia disorder. The characteristics that distinguish between the similarly distressed subtypes 2 and 3 most are more strongly reduced positive affect (d=1·55) and more strongly reduced positive rumination (d=1·55) in subtype 3 relative to subtype 2 (both p<0·0001).

209 (20%) participants were classified in subtype 4, and 161 (15%) participants were classified in subtype 5; participants in both subtypes showed low general distress but can be distinguished by their profiles (figure 3.3C). Participants in subtype 4 showed a longer duration of insomnia response to life events (d=0·94) and more frequent childhood trauma (d=0·82) and fatigue (d=0·60) relative to controls (from which they differed by >0·5 of a standard deviation; p<0·0001 for all three). Subtype 4 can be termed slightly distressed, high reactive insomnia disorder because of the long-lasting insomnia response after a life event.

By contrast, participants classified in subtype 5 scored about 0·5 of a standard deviation lower than control participants on both the duration (d=–0·64) and severity (d=–0·51) of insomnia response to life events, on childhood trauma (d=–0·41), and on rumination (d=–0·55; p<0·0001 for all four). However, relative to the overall low level of distress in participants classified in subtype 5, they scored higher than control participants on reduced behavioural activation (d=0·59), reduced experience of pleasure (d=0·46), and fatigue (d=0·43; p<0·0001 for all three). Subtype 5 can be termed slightly distressed, low reactive insomnia disorder. The characteristics that discriminate the similarly distressed subtypes 4 and 5 most are duration (d=1·68) and severity (d=1·04) of insomnia response to life events, and childhood trauma (d=1·11; p<0·0001 for all three), which are less frequent in participants with subtype 5. Further details of these classifications are shown in the supplementary table A.8.

Lasso regularisation selected the 19 most discriminating characteristics for the ITQ (supplementary section A.1.2 and figure A.1). The selection correctly classified 904 (86%) of 1046 original participants, with high posterior probabilities (0·90–0·97).

Use of the ITQ to classify 251 new participants also resulted in high posterior probabilities (0·92–1·00) and low misclassification (10%). The robustness of a specific five-class solution was verified in this non-overlapping cohort. Again, as compared with latent class analysis models with more or fewer subtypes, a five-class solution was optimal, as indicated by the lowest Bayesian information criterion (figure 3.2B) and excellent posterior probabilities (0·99–1·00) and misclassification (4·5%).

215 (21%) of 1046 participants who were reassessed 4·8 (SD 1·6) years later maintained their subtype at a probability of 0·87, indicating a high stability of these subtypes (table 3.2). Participants who were originally classified as highly or moderately distressed subtypes had high probabilities (0·86–0·89) of maintaining their subtype after an average of 4·8 years. The consistency of subtypes between baseline and follow-up was more modest for those who were first classified in subtypes 4 (0·67) or 5 (0·44). However, participants who were

Table 3.2: Probability of participants maintaining their insomnia disorder subtype between baseline and 4·8 (SD 1·6) years later, based on their responses to the Insomnia Type Questionnaire.

	Subtype 1 at follow-up	Subtype 2 at follow-up	Subtype 3 at follow-up	Subtype 4 at follow-up	Subtype 5 at follow-up
Subtype 1 at baseline	0·87	0·12	0	0	0
Subtype 2 at baseline	0	0·86	0	0·14	0
Subtype 3 at baseline	0	0·01	0·89	0·10	0
Subtype 4 at baseline	0	0·01	0·05	0·67	0·27
Subtype 5 at baseline	0	0·09	0·09	0·37	0·44

Table 2: **Probability of participants maintaining their insomnia disorder subtype between baseline and 4·8 (SD 1·6) years later, based on their responses to the Insomnia Type Questionnaire.**

originally classified in subtype 4 or 5 switched almost exclusively to the other slightly distressed subtype: those classified as subtype 4 had a probability of 0·94 that they would maintain a slightly distressed subtype (4 or 5) and those classified as subtype 5 had a probability of 0·81 that they would maintain a slightly distressed subtype (4 or 5).

Although the current severity of the three key insomnia complaints of difficulty initiating sleep, difficulty maintaining sleep, and early morning awakening did not differ between subtypes (table 3.1), their developmental onset differed markedly. Most notably, half of the participants classified in subtypes 1 and 2 reported difficulty initiating sleep by their teenage years but, in participants classified in subtypes 4 and 5, half of the participants reported difficulty initiating sleep only by age 40 years (figure 3.4; supplementary section A.2.1). Subtypes 1 and 2 thus both represent more participants with insomnia disorder that might conventionally be labelled idiopathic insomnia.

The proportion of participants with comorbid sleep disorders (table 3.1) did not differ across subtypes, except for recurrent nightmares and confusional arousals, which were both highest in subtype 1 and lowest in subtype 5. The proportions of participants classified within each subtype who reported diseases in the main ICD-10 categories, including mental and behavioural disorders, are also shown in table 3.1. Two main categories were differentially represented between subtypes: diseases of the nervous system were most frequent in participants classified in subtype 5 and least frequent in participants classified in subtype 2, and symptoms not elsewhere classified were most frequent in participants classified in subtype 1 and least frequent in participants classified in subtype 5. Four mental and behavioural disorder subcategories (mood, anxiety, personality, and childhood onset) were differentially represented across subtypes, mostly driven by a high prevalence of these disorders in participants classified in subtype 1.

The prevalence of current and lifetime depression differed markedly across subtypes (both $\chi^2(4)>110$; both $p<0{\cdot}0001$; table 3.1) and were most frequent in participants classified in subtype 1, who also reported the greatest frequency

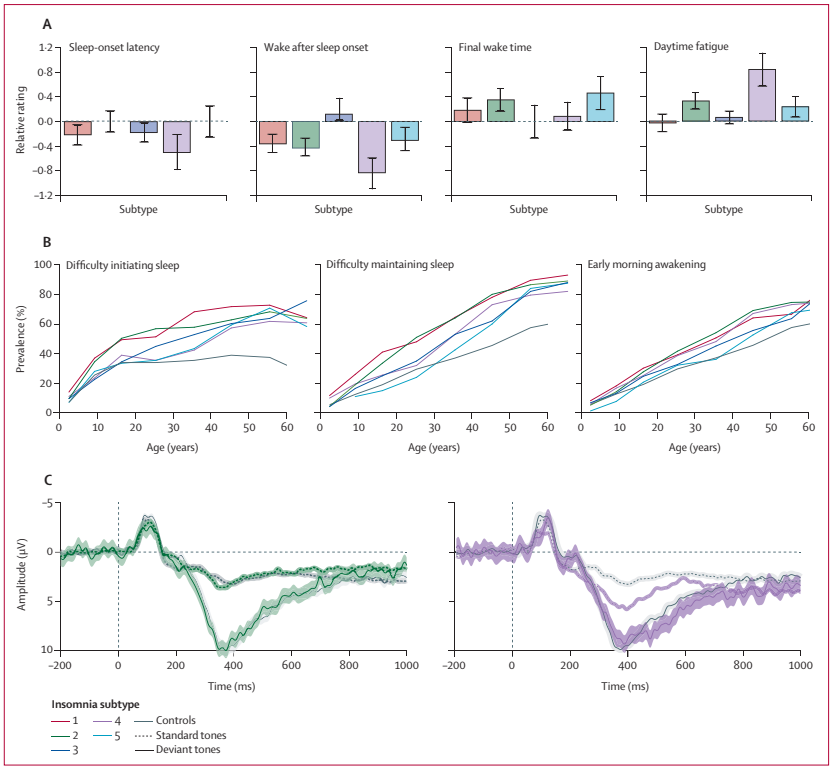

Figure 3.4: Clinical relevance of insomnia disorder subtypes. (A) The effect of incidental benzodiazepine use the preceding night on sleep and daytime fatigue (n=112). (B) Percentage of participants with insomnia subtypes (n=796) and control participants (n=1024) who reported any difficulty initiating or maintaining sleep or early morning awakening. (C) Auditory event-related potentials for standard tones and deviant tones that were recorded during an auditory oddball task for participants with insomnia disorder subtypes 2 (n=16) and 4 (n=13) and control group participants (n=31).

of recurrent nightmares, in accordance with previously reported associations of insomnia, nightmares and depression [24]. Notably, current depression was three times less prevalent in participants classified in subtype 2 (16 [6%] of 267 participants) than in participants classified in subtype 3 (25 [19%] of 134 participants), despite their similar indications of general distress (figure 3.3). There was up to a five times difference between subtypes in the lifetime risk of depression (table 3.1).

Incidental benzodiazepine intake affected difficulty initiating sleep, difficulty maintaining sleep, early morning awakening, and fatigue differently across the five subtypes ($F(16,406)=1{\cdot}75$; $p=0{\cdot}04$). The most notable differences with benzodiazepine intake were reported in difficulty maintaining sleep, which improved most in participants classified in subtypes 2 and 4 but not in subtype 3 (figure 3.4; supplementary section A.2.2.1).

CBT for insomnia affected the ISI scores of patients differently between subtypes 2 and 4 (supplementary section A.2.2.2). Compared with control group patients who were awaiting CBT, this treatment ameliorated difficulty initiating sleep significantly more in subtype 2 (mean change in score –0·8 [SD 1·9]; p=0·0003) than in subtype 4, where it was ineffective (0·1, [SD 1·5]; p=0·69). This disparity in response to CBT was also reflected in the total ISI score (–5·5, SD 7·8; p<0·0001; vs –3·1, SD 7·3; p=0·003 in type 4). Notably, the underrepresentation of subtypes 1, 3, and 5 in this sample illustrates how commonly differing selection criteria can strongly affect the subtype distribution of the study. We found that strict criteria on mood symptoms impeded inclusion of participants in subtypes 1 and 3 from participation in this study, whereas a low prevalence and age exclusion criteria impeded inclusion of participants of subtype 5.

Compared with control group participants without sleep complaints, the ERP to standard tones exclusively showed a stronger positive deflection during a wide late period of information processing up to at least 1000 ms after the tone was played in participants classified in subtype 4, and this finding was significantly different from controls at 273–348 ms (p=0·038), 361–493 ms (p=0·014), and 724–1000 ms (p=0·004; figure 3.4). ERPs of subtype 2, by contrast, were indistinguishable from those of control group participants. These findings indicate hyperreactive late processing specifically in subtype 4, who appeared to experience even standard tones as more salient (as indicated by the P300 potential amplitude) and emotionally relevant (as indicated by the late positive potential amplitude), in agreement with their questionnaire-based label of being highly reactive [23].

3.4 DISCUSSION

In our study, we identified five insomnia disorder subtypes that were differentiated by biologically based traits and life history. The subtypes that we identified were a highly distressed type that was characterised by distress across all domains; two moderately distressed types, one of which was reward sensitive and the other of which was reward insensitive; and two slightly distressed subtypes, one of which showed high reactivity to life events and the other of which showed low reactivity. Subtyping was stable over time, clinically relevant, and biologically meaningful, as indicated by enhanced salience and emotion signalling in the brain of participants classified as type 4. Subtyping is feasible with a concise set of questions that we have made available (see `https://tfblanken.github.io/portfolio/1_ITQ/`), including automated scoring (see `https://tfblanken.shinyapps.io/itqapp/`).

The subtypes were not primarily distinguished by existing clinical demarcations such as difficulty initiating sleep, difficulty maintaining sleep, or early morning awakening, nor by comorbid sleep disorders. Rather, subtypes emerged as specific, multivariate profiles of stable characteristics that were not directly

related to sleep but were relevant to insomnia [19]. High or low scores on single variables were not unique to our insomnia subtypes, but the fingerprints of specific combinations of score levels on these characteristics are unique to the subtypes. Ancillary analyses (supplementary section A.2.3) showed that none of the five subtypes resembled subtypes that can be found with bottom-up subtyping of people without insomnia.

The stability of subtypes over several years that we found was notable. Most participants were identically classified 4·8 (SD 1·6) years after their initial subtyping (at a probability of 0·87), which compares favourably to previous clinical subtyping that showed poor reliability [15] and instability over even a brief period (33% over 4 months) [14]. To our knowledge, our insomnia disorder subtypes are the first to fulfil the primary requirement of stability that is necessary to find differential trajectories for, biomarkers of, and treatment responses in insomnia disorder.

Clinically, our identified subtypes provide precision targets to improve cognitive, emotional, and behavioural interventions. For example, because a meditation intervention lowers pre-sleep arousal [25], this treatment could particularly be recommended for people with insomnia disorder of subtypes 1, 2, and 3, which are characterised by high pre-sleep arousal. Interventions that aim to improve positive affect and happiness [26] could be evaluated for people with insomnia subtypes 3 and 5, who showed a disproportional reduced positive affect or experience of pleasure. Finally, sleep problems related to childhood adversity, which was most prevalent among participants with subtypes 1 and 4, could require trauma therapy rather than CBT for insomnia only [27].

The clinical relevance of subtyping reaches beyond insomnia. Possibly related to a strong genetic overlap [5], insomnia is a primary risk factor for depression [8]. The Global Consortium for Depression Prevention stated that the best chance to combat the global burden of depression is to identify people who run the highest risk and to provide them with preventive interventions [28]. Supported by the strong differences in current comorbid and lifetime depression, our subtyping approach could enable us to identify people with insomnia disorder who are most at risk for developing depression, and to prioritise their inclusion in preventive trials. Participants with subtype 1 insomnia scored highly on several symptoms of depression and showed the highest risk of lifetime depression. However, near half of participants classified in subtype 1 had never experienced depression.

This finding is of considerable clinical interest for at least two reasons. First, people with subtype 1 insomnia disorder might have subclinical depression, and people with this subtype are most suitable to select for intervention programmes that aim to prevent depression. Use of our ITQ could facilitate such selection. Second, there could be an unknown factor that makes the unaffected half of our participants with subtype 1 resilient to depression despite a high risk.

We illustrated how differentiation between subtypes 2 and 4 could propel the identification of biomarkers that would otherwise remain hidden by heterogeneity. ERPs deviated from the values in controls in participants with subtype 4

insomnia but not subtype 2 insomnia. The high amplitude late positive potential of the ERP in subtype 4 could relate to polymorphisms in the β1-receptor gene and response to betablockers, thus providing an example of a drug-targetable biomarker [23]. More specifically C/C homozygotes for the G1165C polymorphism in the β1-adrenergic receptor showed a larger late positive potential amplitude than G/C heterozygotes and G/G homozygotes. Moreover, our ERP finding supports consistency of labelling subtype 4 as reactive across psychometric traits and neurophysiology, thus meeting an important goal of the Research Domain Criteria [29].

Finally, we constructed and validated our ITQ, including automated analysis, to facilitate subtyping in future studies on insomnia. This subtyping can be done online and will accelerate insight into underlying causes and biomarkers of insomnia disorder and the development of better, more personalised treatments.

Some limitations should be mentioned. First, although five subtypes were found to be optimal in both the original sample and the second, nonoverlapping validation cohort, we cannot exclude the existence of other subtypes – for example, among people who do not volunteer for online assessment – because the NSR did not sample randomly from the general population. We deliberately did not exclusively sample from sleep clinics because, unfortunately, insomnia often goes unnoticed in general practice [16]. Sleep centre-based studies overrepresent complex insomnia in people who are more affected, but the NSR reaches a more diverse population of people with insomnia disorder. A possible disadvantage of case-control comparisons from the NSR could be that the control group might have been biased to include more people with a special interest in sleep or helping science. Therefore, replication of our study in a strict population-based sample will be useful.

Second, we defined probable insomnia disorder by an ISI cut-off score of 10. Although this cut-off has been validated several times [5,21] and the ISI has been validated for web-based assessment [30], it could be asked whether the cut-off can indicate insomnia of sufficient severity to warrant independent clinical attention and thus a separate DSM-5 diagnosis. A randomised trial [31] in patients with major depressive disorder used the same ISI cut-off of 10 to define comorbid insomnia; this study found that clinical attention to insomnia of this severity was highly valuable because treatment reduced insomnia and depression. This finding adds to the clinical validity of the ISI cut-off. The traditional approach to treat only the other morbidity, with the expectation that insomnia will resolve, is not regarded as the most appropriate approach [17]; treatment of both conditions simultaneously might improve the outcomes for both conditions [32]. In support of this hypothesis, a meta-analysis [33] that included 17 studies that used ISI scores supported treatment of insomnia in conjunction with comorbid psychiatric and medical conditions.

Finally, traits that we have not assessed could discriminate yet other subtypes. Although we cannot exclude this possibility, it should be noted that we included an unprecedentedly large number of stable characteristics. Moreover, subtypes were defined by several characteristics, suggesting at least some robustness

for unobserved characteristics. Within these limitations, the identification of subtypes enables important possibilities for pursuing subtype-specific risks, biomarkers, or treatment responses.

In summary, we found that insomnia disorder can be classified into robust subtypes that can be discriminated by multivariate profiles of traits of affect and personality and life history. Subtyping was highly consistent after 4·8 years of follow up, results could be replicated in a second, non overlapping cohort, and the subtypes could reliably be assessed with the ITQ. Insomnia subtyping paves the way for studies that aim to prevent depression, resolve in consistencies in and reduce heterogeneity of insomnia, and reveal differential causes of and develop better tailored personalised treatment for insomnia disorder.

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COMMENTARIES AND REPLY

3.6 SUMMARY OF COMMENTARIES

Below a summary of the commentaries is placed. For the original commentaries, see supplementary section A.5.

3.6.1 *Ferini-Strambi et al.*

Ferini-Strambi and colleagues discuss some methodological, clinical, and practical concerns. First, they wonder whether the interrelations between the observable indicators could be accurately assessed using exclusively self-report measures, or whether the findings are biased by shared method variability. Second, because the diagnosis of insomnia is based solely on subjective criteria, it is currently unknown whether other pathological conditions and subtypes could be revealed by using concomitant objective and subjective assessments such as in-depth clinical evaluation and polysomnography. Third, the questionnaire and associated web-based tool to subtype patients was deemed too complex to be used in clinical practice. The authors concluded with the challenge to integrate objective and subjective evaluation of sleep profiles to identify insomnia patients that are at high-risk for medical consequences.

3.6.2 *Hirakawa*

Hirakawa zoomed in on the highly distressed subtype 1 – their comorbidities, and development of sleep complaints – and suggested whether some of the participants with this subtype could have also been diagnosed with bipolar spectrum disorder. The observed comorbidities of mood problems and the high prevalence of sleep disturbances already in the teenage years could be in line with the pathophysiology of bipolar disorder. Hirakawa suggested to re-analyze the data and evaluate the percentage of people in subtype 1 that developed sleep complaints by their teenage years and then continued to develop a depression or bipolar disorder. Hirakawa suspected that subtype 1 could this way be subdivided into two additional groups based on the presence of bipolarity.

3.7 REPLY

We are grateful for the opportunity to clarify our new insomnia subtypes [1]. Luigi Ferini-Strambi and colleagues invite us to address common method bias. Bias by online assessment, if any, cannot underlie differences among subtypes

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and controls because the bias applies to all equally. Whether participants would be similarly grouped together if subtypes were sought in objective sleep electroencephalogram (EEG) features, rather than in subjectively reported traits, is a different question. We do not propose our subtyping method as a replacement for sleep EEG recordings aimed at revealing other pathological sleep conditions. Polysomnography can be essential for the diagnosis of comorbid sleep conditions, which are equally likely across subtypes [1]. EEG, however, reflects only a small part of the rich repertoire of neuronal activity in the brain. Contents of consciousness remain hidden. People can ruminate while brain waves suggest sound sleep [2]. Genome-wide association studies [3] suggest key involvement of the axonal part of neurons and of specific cell types in subcortical areas in insomnia, which do not necessarily leave any trace in sleep EEG.

Indeed, past attempts to subtype insomnia based on sleep features failed: they lacked stability. An addition to top-down defined subtypes is so-called short sleep insomnia, characterised by fewer than 6 hours of sleep. The suggested high cardiovascular risk and treatment resistance of this subtype are equivocal [4,5]. Again, stability is poor; of those people with insomnia who were classified as short sleepers after a first night, 68% did not meet the criterion already the next night [4]. By contrast, people with insomnia who were classified using our data-driven subtyping [1] had a probability of 0·87 of maintaining their subtype across 5 years.

The success of our new subtyping method might relate to the un- precedented variety of assessed traits, each one selected on relevance to insomnia, and most of them shown to reflect individual differences in molecular signalling pathways and brain cells and circuits [1]. Our high- dimensional approach possibly gave us the sensitivity to detect distributed brain differences that could distinguish various insomnia subtypes and controls. As suggested by Ferini-Strambi and colleagues and exemplified in our work [1], more advanced methods of EEG and other objective measures could add to distinguishing subtypes and to our understanding of underlying mechanisms.

Is it feasible for clinicians to assess all these traits to subtype their insomnia patients? In fact, this assessment can be done in a fraction of the time needed to record and score sleep EEG. Aware of the time constraints clinicians face, we are preparing a free online multilingual tool for unsupervised self-assessment of subtypes by patients, not requiring any time by clinicians.

Hirofumi Hirakawa would like to know the onset of insomnia relative to the first signs of bipolarity diagnosed in eight patients with the subtype of highly distressed insomnia. Insomnia commenced earlier in three, simultaneously in four, and later in one. Because multimorbidity is the rule rather than the exception, generating a separate subtype for all possible combinations of disorders, let alone the sequence of their onsets, is impractical. Importantly, we do not propose a separate diagnosis for each of the insomnia subtypes either. Rather, we hope that our novel subtyping approach aids research to elucidate the distributed brain differences among subtypes and controls. Differently distributed deviations all lead to the final common path of insomnia, but the best way back

to sound sleep could require precision intervention that is subtype-dependent and personalised.

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Part II

INSOMNIA AND DEPRESSION

There is a close link between insomnia and despair.
The loss of hope comes with the loss of sleep.

— E.M. Cioran, "Man, the Insomniac Animal"

4

PROSPECTIVELY: NETWORK OUTCOME ANALYSIS

ABSTRACT

STUDY OBJECTIVES Major depressive disorder (MDD) is the leading cause of disability worldwide. Its high recurrence rate calls for prevention of first-onset MDD. While meta-analysis suggested insomnia as the strongest modifiable risk factor, previous studies insufficiently addressed that insomnia might also occur as a residual symptom of unassessed prior depression, or as a comorbid complaint secondary to other depression risks.

METHODS N=768 participants from the Netherlands Study of Depression and Anxiety who were free from current and lifetime Major Depressive Disorder were followed-up for four repeated assessments, spanning six years in total. We performed separate Cox Proportional Hazard analyses to evaluate whether baseline insomnia severity, short-sleep duration, and individual insomnia complaints prospectively predicted first-onset MDD during follow-up. The novel method of Network Outcome Analysis (NOA) allowed us to sort out whether there is any *direct* predictive value of individual insomnia complaints among several other complaints that are associated with insomnia.

RESULTS Over six-years follow-up, N=141 (18.4%) were diagnosed with first-onset MDD. Insomnia severity but not sleep duration predicted first-onset MDD (HR=1.11, 95%-CI: 1.07-1.15), and this was driven solely by the insomnia complaint 'difficulty initiating sleep' (DIS) (HR=1.10, 95%-CI: 1.04-1.16). NOA likewise identified DIS only to directly predict first-onset MDD, independent of four other associated depression complaints.

CONCLUSIONS We showed prospectively that DIS is a risk factor for first-onset MDD. Among the different other insomnia symptoms, the specific treatment of DIS might be the most sensible target to combat the global burden of depression through prevention.

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STATEMENT OF SIGNIFICANCE

The high prevalence and recurrence rate of major depressive disorder (MDD) stress the utmost importance of prevention of *first-onset* MDD. Using the novel method of Network Outcome Analysis (NOA), we identified that, among insomnia complaints, only 'difficulty initiating sleep' is an independent and primary predictor of first-onset MDD. Crucially, these findings are of high clinical relevance, as cognitive behavioural therapy for insomnia is highly effective in improving difficulty initiating sleep. Targeting specifically difficulty initiating sleep in the treatment of insomnia might aid to combat the global burden of MDD by means of prevention.

4.1 INTRODUCTION

Major depressive disorder (MDD) is the leading cause of disability worldwide [1] and prevalence rates continue to rise [2,3]. Because the probability of recurrence is high [4], the prevention of MDD would be more efficient than its treatment. It is therefore of utmost importance to determine primary modifiable risk factors for the development of first onset major depressive disorder (MDD) [5]. Knowing these targets is a prerequisite to identify vulnerable individuals and to optimize attempts to prevent rather than treat depression [6]. Insomnia has often been suggested to be a primary modifiable risk factor of depression [7,8]. The identification of insomnia as an *independent* risk factor for *first-onset depression* is however complicated by at least two challenges.

A first challenge, and shortcoming of most previous studies that investigated insomnia as a risk factor for depression, is that while current depression is often excluded, the lifetime history of a depression diagnosis is rarely assessed. Because *prior* depression is among the strongest risk factors for depression, it is difficult to disentangle *de novo* risk factors from residual symptoms. Importantly, insomnia is the most common residual symptom of depression [9]. Therefore, only if a lifetime history of a depression diagnosis can be excluded, it can be ruled out that prior depression rather than insomnia is predictive for a future depressive episode.

A second challenge is that insomnia complaints can be considered a symptom of both insomnia and MDD. Therefore, someone who suffers from insomnia also suffers from one symptom of MDD according to diagnostic criteria [10], which might explain its predictive effect. The predictive value of insomnia for first-onset MDD may thus be nonspecific, indistinguishable from other depression complaints. Although several studies investigated whether baseline depression symptoms predict MDD onset [e.g., 11-14], none of these previous studies took into account that the depression symptoms are themselves related and that, as a consequence, some symptoms might only predict MDD via

their relations to other symptoms. How to validly determine the importance of insomnia amidst this set of correlated symptoms has so far remained enigmatic.

To overcome these challenges we performed a six year study with three follow-up assessments in a large sample carefully selected to be free from both a current and a lifetime prior diagnosis of MDD. We moreover answered the pressing need to determine primary risk factors of first-onset MDD among multiple possibly predictive symptoms of insomnia and depression, by applying a novel method for symptom network analysis, which we will refer to as Network Outcome Analysis (NOA).

4.2 METHODS

4.2.1 *Participants*

We carefully selected participants from the Netherlands Study of Depression and Anxiety (NESDA), a multi-site longitudinal study including four repeated assessments (T0-T3), spanning six years in total [15]. Included participants were strictly without a current or prior lifetime Major Depressive Disorder according to the DSM-IV, determined using the Composite International Diagnostic Interview (CIDI) [16], and for whom a CIDI at each of three follow-up measurements was completed. The 768 included participants were between 18 and 65 years of age (M=41.1 years, SD=14.4 years), and 482 (62.7%) were female.

4.2.2 *Measures*

At T0, insomnia severity, sleep duration, and severity of individual depression symptoms were assessed.

Insomnia severity was assessed using the Women's Health Initiative Insomnia Rating Scale (IRS) [17]. The IRS contains five items on sleep problems (i.e., trouble falling asleep, waking up during the night, waking up earlier than planned, and troubles getting back to sleep) and sleep quality during the past month (scale 0-4), for which a total score can be computed (range 0-20).

Sleep duration was assessed by asking subjects to estimate the average hours of sleep per night during the past month, where $\leq$6 hours was coded as short sleep duration. The risk of depression by conveyed by short sleep is less clear than the risk imposed by insomnia. A meta-analysis of prospective studies suggests that short sleep increases the risk depression with an odds ratio (OR) of 1.31 [18], while meta-analyses on the risk of MDD imposed by insomnia reported a range of OR = 2.10-2.60 [7,8]. Despite the lower risk, we still considered it important to include short sleep in our analyses, because short sleep has also been shown to predict insomnia chronicity [19], and chronic rather than acute insomnia adds to the risk of first-onset depression [20]. It has indeed been suggested that the risk on depression is largest for people suffering from both insomnia and short sleep [21].

Table 4.1: DSM-5 criteria of MDD (left two columns), corresponding IDS items (middle two columns), and included nonclinical complaint abbreviation (right).

DSM-5 MDD criteria		IDS item		Abbreviated
Criterion	Description	Item	Description	symptom
A1	Depressed mood	5	Feeling sad	dep
A2	Loass of interest/pleasure	19	General interest	int
A3	Weight/appetite change	11	Decreased appetite	app
		12	Increased appetite	
		13	Decreased weight	wei
		14	Increased weight	
A4-a	Insomnia	1	Falling asleep	dis
		2	Sleep during the night	dms
		3	Waking up too early	ema
A4-b	Hypersomnia	4	Sleeping too much	hyp
A5-a	Psychomotor retardation	23	Feeling slowed down	ret
A5-b	Psychomotor agitation	24	Feeling restless	agi
A6	Fatigue or loss of energy	20	Energy level	ene
A7	Guilt/worthlessness	16	View of myself	gui
A8	Concentration	15	Concentration/decision making	con
A9	Suicidality	18	Thoughts of death or suicide	sui

Severity of baseline depression complaints were assessed using 30 items of the Inventory of Depressive Symptomatology (IDS), with items rated on a 4-point scale (0-3) [22]. Following Van Borkulo et al. [23] we used the items of the IDS that mapped onto the nine criteria of a DSM-5 MDD diagnosis, see Table 4.1. Some DSM-5 criteria are represented by multiple IDS items, resulting in an initial selection of 16 items. However, two sets of two items, respectively inquiring changes in weight and appetite, were mutually exclusive, resulting perfect negative relations between the two variables. We followed Van Borkulo et al. [23] in recoding each of these two sets of two items in to two single items on appetite and weight change, resulting in a total of 14 items. . Finally, note that all nonclinical depression complaints at baseline, including insomnia, are assessed using the IDS, see Table 1.

4.2.3 *Statistical Analyses*

4.2.3.1 *Cox Proportional Hazard analysis*

Using a Cox Proportional Hazard models we first investigated the effect of baseline insomnia severity (IRS) on first-onset MDD. Second, we investigated whether short-sleep duration has an additional effect. Third, as insomnia is defined by different nocturnal complaints that are covered by separate IRS items, we assessed whether specific insomnia symptoms are most predictive of first-onset MDD using models with the individual IRS items instead of the IRS summary score. Analyses were performed in R (version 3.5.0) using the package 'survival'.

4.2.3.2 *Network Outcome Analysis*

We subsequently addressed the possible confounding issue that insomnia commonly co-occurs with a vast variety of other complaints. Therefore, the predictive value of insomnia complaints for first-onset MDD could be nonspecific, indistinguishable from the predictive value of other complaints. Network models provide a powerful framework to study the interactions among symptoms and their role in the development and maintenance of psychiatric disorders [24]. Using network analysis we can estimate the unique association between pairs of symptoms, while controlling for the state and associations of all other symptoms [25,26]. Accordingly, a connection (edge) between two symptoms (nodes) in the network structure, provides evidence for a direct rather than indirect association. We recently innovated the network analysis framework by demonstrating the possibility and use of including the presence or absence of an intervention [25]. Here, we employed a similar key innovation [26], which we propose to call Network Outcome Analysis (NOA), in which we include the outcome 'first-onset MDD' during the six-year follow-up as a variable in the network. Accordingly, NOA allowed us to distinguish symptoms that predict first-onset MDD *directly* from symptoms that do so indirectly through their association with directly related symptoms.

ESTIMATION For the Network Outcome Analysis (NOA) we estimated a Mixed Graphical Model [27] in which we included all baseline depression symptoms (Table 4.1) as continuous and the first-onset MDD outcome as binary (0: no first-onset MDD; 1: first-onset MDD; FO-MDD). In the network, the symptoms are presented as nodes (IDS items as circles, FO-MDD indicator as square) that are connected by edges that encode the unique association among two variables after controlling for all other variables in the network. In estimating the networks, we used LASSO regularization to prevent the inclusion of spurious edges due to sampling variation [28], see supplement section B.1.2.1 for details. Finally, we assessed the accuracy of the estimated networks [29,30], see supplement B.1.2.2 for details. These analyses were performed in R (version 3.5.0) using the packages 'qgraph', 'bootnet', and 'mgm'.

INTERPRETATION In the network, the edges represent the unique association between two variables, while controlling for all the other variables in the network (i.e., conditional dependence relationships) [28]. Any edge between a symptom and the FO-MDD indicator variable is thus indicative of the unique predictive value of that symptom, while controlling for all the other baseline depression symptoms. Because the baseline depression symptoms temporally precede the first-onset depression during follow-up, we know that the symptoms can lead to depression onset but not vice versa (i.e., depression onset later in time cannot affect symptom levels at baseline). An edge between a symptom and the first-onset depression outcome thus indicates that symptom directly

and uniquely predicts first-onset depression, while controlling for the other symptoms.

The presence and strength of an edge is proportionate to regression coefficients [28]. At the same time, and unlike regression analysis, the network also models how the different symptoms predict one another. The network thus maps out the linear prediction and multicollinearity among all variables. Accordingly, it can provide insight into predictive mediation: the network might reveal variables that are only indirectly related through a third variable (e.g., A-B-C), which indicates that, even though A and C might be correlated, any predictive effect from A to C or vice versa is mediated by B.28 The network model thereby provides a unique opportunity to investigate direct and indirect effects from the baseline depression symptoms to first-onset MDD.

EVALUATION To evaluate the symptoms that were identified by NOA as direct predictors of first-onset MDD, we compared the area under the receiver operator characteristic (ROC) curve predicting first-onset depression using the sum score of these direct predictors versus the sum score of all predictors. This analysis was performed in R (version 3.5.0) using the package 'pROC'.

4.3 RESULTS

Of the 768 participants that were initially without current or prior lifetime MDD, 141 (18.4%) were later diagnosed with first-onset MDD: 75 between To and T1, 46 between T1 and T2, and 20 between T2 and T3. Participants who developed MDD during the six-year follow-up period were slightly, but non-significantly, younger (39.1 versus 41.5 years, p=.09) and were more likely to be female, (marginally significant; 70.2% versus 61.0% female, p=.05), as compared to participants who did not develop MDD.

Cox proportional hazard analysis showed that the odds of first-onset MDD increased by 11% (HR=1.11, 95%-CI: 1.07-1.15) with every 1-point increase of the IRS score (observed range: 0-20 points). Thus, as compared to participants without insomnia complaints (IRS=0), participants scoring at the insomnia cutoff of IRS=9 were 2.6 times more likely to develop first-onset MDD, and participants with the most severe insomnia complaints (IRS=20) were 8.1 times more likely. This result did not change appreciably when adding age, sex, and presence of any anxiety disorder diagnosis at baseline as covariates (HR=1.10, 95%-CI: 1.04-1.16). Including short-sleep duration in the model did not affect the risk for first-onset depression: The 22% that indicated to have slept 6 hours or less over the past month did not have an increased risk (HR=0.95, 95%-CI: 0.35-2.63), also not in interaction with insomnia severity (HR=0.99, 95%-CI: 0.91-1.10).

Performing Cox proportional hazard analysis using the individual IRS items revealed that the predictive effect of insomnia on first-onset MDD was driven solely by the item "did you have trouble falling asleep" (HR=1.33, 95%-CI: 1.12-

1.57; observed range: 0-4). As compared to those without difficulty initiating sleep (item score 0), people experiencing trouble falling asleep 3-4 times or >4 times a week were respectively 2.3 times or 3.2 more likely to develop first-onset MDD. Importantly, none of the other sleep complaints - including nocturnal and early morning awakening – significantly increased the risk of first-onset MDD.

NOA identified five nonclinical complaints at baseline to directly predict first-onset MDD while controlling for the other complaints: energy level, concentration/decision making, feeling sad, feeling restless, and difficulty falling asleep. Predictive effects of other complaints were estimated to be indirect (see Figure 1). The results did not change when adding age, sex, and presence of any anxiety disorder diagnosis at baseline into the analyses, see supplementary section B.1.3. The area under the receiver operating characteristic (ROC) curve revealed that the sum score of the five direct complaints captures all relevant information to predict first-onset MDD (AUC=0.76, 95%-CI: 0.71-0.81). Adding the other nine complaints did not improve the prediction accuracy (AUC=0.75, 95%-CI: 0.71-0.80).

4.4 DISCUSSION

The ever increasing prevalence rate of major depressive disorder (MDD), already a major contributor of the global burden of disease today, stresses the utmost importance to identify modifiable risk factors. Although it has often been stated that insomnia is such a primary modifiable risk factor [7,8], insomnia is also the most common residual symptom [9], and studies on risks have usually not assessed a prior diagnosis of MDD. Moreover, because insomnia often co-occurs secondary to other symptoms, insomnia might not necessarily be of primary importance. In the current study we overcame these challenges by carefully selecting participants free from lifetime MDD and applying the novel Network Outcome Analysis (NOA) to identify primary risk factors amidst a large number of correlated predictors.

We could reveal that insomnia, and 'difficulty initiating sleep' in particular, is a primary and independent prospective risk factor for first-onset MDD. This predictive effect could not be attributed to an earlier depressive episode, nor to an indirect association via other depression symptoms. These results suggest that 'difficulty initiating sleep' might be a viable target for risk detection and prevention of MDD.

While the relationship between insomnia and depression onset has been studied extensively [7,8], the current prospective study is the first to address both the possibility that insomnia complaints could represent a residual symptom from prior depression, as well as the issue of possible confounding through its connection to other baseline complaints. Another particular strength is that the gold standard WHO-recommended Composite International Diagnostic Interview was used to diagnose depression. A final strength of the current

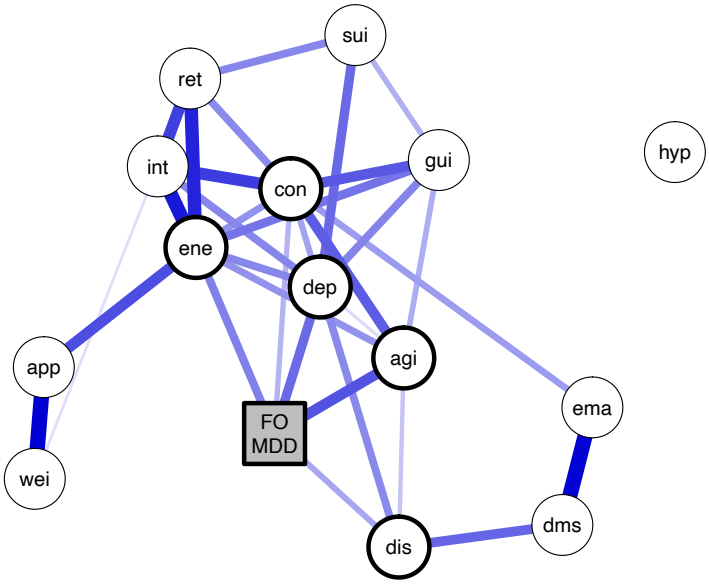

Figure 4.1: Regularized network showing the conditional dependence relations among the baseline depression symptoms (circles) and first-onset MDD (FO MDD) during the six-year follow-up period (yes or no; square). Edges represent conditional dependence relations among the variables and capture unique effects that remain after controlling for all the other variables in the network. The thickness and colour saturation of the edges corresponds to the strength of the association. In this network, all associations are positive. The five symptom nodes that are directly predictive of first-onset MDD are indicated by thicker outlined circles. Abbreviations: agi = psychomotor agitation; app = appetite change; con = concentration problems; dep = depressed mood; dis = difficulty initiating sleep; dms = difficulty maintaining sleep; ene = fatigue or loss of energy; ema = early morning awakenings; FO-MDD = first-onset depression; gui = feelings of guilt or worthlessness; hyp = hypersomnia; int = loss of interest; ret = psychomotor retardation; sui = suicidal thoughts; wei = weight change.

study is that we compared the prospective risk factor of insomnia to that of other depression symptoms.

The importance of our findings is stressed by the high prevalence of MDD [1], its increasing associated costs [31], and the pressing need to prevent *first-onset* MDD because of the high recurrence rates [4,6]. In order to prevent rather than treat MDD, this study meets the need to identify modifiable risk factors of *first-onset* depression. The identification of 'difficulty initiating sleep' as a risk factor is particularly promising, because a recent meta-analysis showed that cognitive behavioural therapy, the treatment of choice for insomnia, is highly effective [32]. This intervention moreover improves mood [33,34,35] which we also identified as a direct risk factor. The current findings call for studies to evaluate whether treatment of 'difficulty initiating sleep' might *prevent* first-onset MDD.

We also evaluated whether short-sleep duration added to the risk to develop first-onset MDD. Contrary to suggestions that insomnia together with short sleep duration is the most severe phenotype, short sleep duration itself or in combination with insomnia did not increase the risk for developing first-onset MDD. Since we only used a subjective measure of short-sleep duration, we cannot fully exclude the possibility that short-sleep duration adds to the risk of MDD. This finding does however align with earlier studies that showed that short-sleep duration was a weaker predictor of MDD than insomnia.

Another factor that might increase the prospective risk for depression is chronotype, as evening types are more prone to also suffer from complaints of both insomnia and depression [36,37]. Unfortunately, chronotype was not assessed at baseline, and could therefore not be incorporated into the analysis. The assessment of chronotype in insomnia is however not without problems, not in the least because the calculation of the mid-sleep phase, which is the most common self-reported measure for chronotype, is intrinsically dependent on the subjectively experienced sleep onset, of which delays will be reported as difficulties initiating sleep [38]. Consequently, difficulties initiating sleep and chronotype will inevitably be correlated. Still, it is unlikely that the association of both a late chronotype and difficulty initiating sleep with the risk of depression is merely due to confounding of these two predictors: in a study on 4948 adolescents, both evening type and insomnia were independently associated with an increased risk of having emotional problems [39]. Future prospective studies would ideally obtain different measures of chronotype [37,40] to sort out the relative prospective risks conveyed by being and evening type and experiencing difficulties initiating sleep.

A notable finding is that particularly 'difficulty initiating sleep', and not the other sleep complaints 'difficulty maintaining sleep' and 'early morning awakening', is predictive for first-onset MDD. This finding was robust across assessment formats and analyses. At least two earlier studies found 'difficulty initiating sleep' to be particularly predictive for depression [41,42]. However, in these studies, lifetime history of depression was not assessed, so the possibility that sleep complaints represented residual symptoms of a prior depression could not be excluded. Moreover, none of these studies diagnosed depression

using clinical interviews. We overcame these limitations and were able to confirm that the effect of difficulty initiating sleep on *first-onset* MDD is robust.

The question may be posed why in particular difficulty initiating sleep is directly predictive, while difficulty maintaining sleep and early morning awakening are only indirectly predictive. An intriguing possibility revealed by the novel NOA approach, is that difficulty initiating sleep is the most direct indicator of an underlying vulnerability. In this interpretation, it is not so much the waking up during the night or early in the morning that is bothersome, but rather the subsequent difficulty of getting back to sleep. Phrased differently, while insomnia undoubtedly involves abundant transitions from sleep to wake [43], the core experienced problem may rather be the difficulty of transitioning from wake to sleep, either at sleep onset or at any time later during the night. Interestingly, our results suggest that especially the presence of such difficulties at the onset of the night convey a vulnerability for first-onset MDD.

To conclude, we identified a robust direct contribution of difficulty initiating sleep to the risk of first-onset MDD. The finding is of high clinical relevance, since this complaint can effectively be treated with cognitive behavioural therapy [32]. Our identification of five primary predictive complaints will benefit the efficiency of studies on other preventive interventions, by defining the best outcome measures and allowing for selection of most vulnerable individuals. Treating difficulties initiating sleep could contribute significantly to combat the global burden of depression by means of prevention [6].

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5

CONCURRENTLY: NETWORK INTERVENTION ANALYSIS

Insomnia and depression are among the most prevalent mental disorders and often co-occur [1]. Insomnia is a primary risk factor for the development of depression [2]. In people with depression, insomnia impedes remission [3,4], while cognitive-behavioral therapy for insomnia (CBTI) accelerates it [5,6]. However, overlap in the symptoms of insomnia and depression obscures the sequential development and order of treatment-induced changes: do CBTI-induced sleep improvements precede alleviation of depres- sion symptoms, or does CBTI affect depression directly?

A possibility to investigate the effect of CBTI on insomnia and depression while taking symptom overlap into account is offered by network models that conceptualize mental disorders as networks of symptoms structured by their associations [7]. Here we introduce Network Intervention Analysis (NIA) as an extension of these models to follow the development of treatment-induced changes in symptoms and their association structure over time, while distinguishing direct and indirect effects.

We applied NIA to identify the sequential development and order of CBTI-induced effects on symptoms of insomnia and depression throughout the course of treatment. We used data from a randomized controlled trial [6] in which participants with symptoms of insomnia and depression received either 5 weeks of CBTI (n = 52) or no treatment (n = 52). Symptoms of insomnia (Insomnia Severity Index) and depression (Patient Health Questionnaire) were assessed at the end of each week, for 10 weeks (before treatment T0–T1, during treatment T2–T6, after treatment T7–T9).

For each week, we estimated a LASSO-regularized network that included a treatment allocation variable in addition to all symptoms. This procedure allowed us not only to follow the sequential development of treatment-induced changes in the severity of individual symptoms, but also to distinguish, at each point in time, the specific symptoms that were most directly affected by treatment and those that were indirectly affected. NIA moreover revealed the sequential development of treatment-induced changes in the network structure of associations by estimating, for each symptom, the proportion of variance that is explained by the other symptoms in the network (called predictability). Details on sample characteristics and the NIA are provided in the supplementary material in appendix C.

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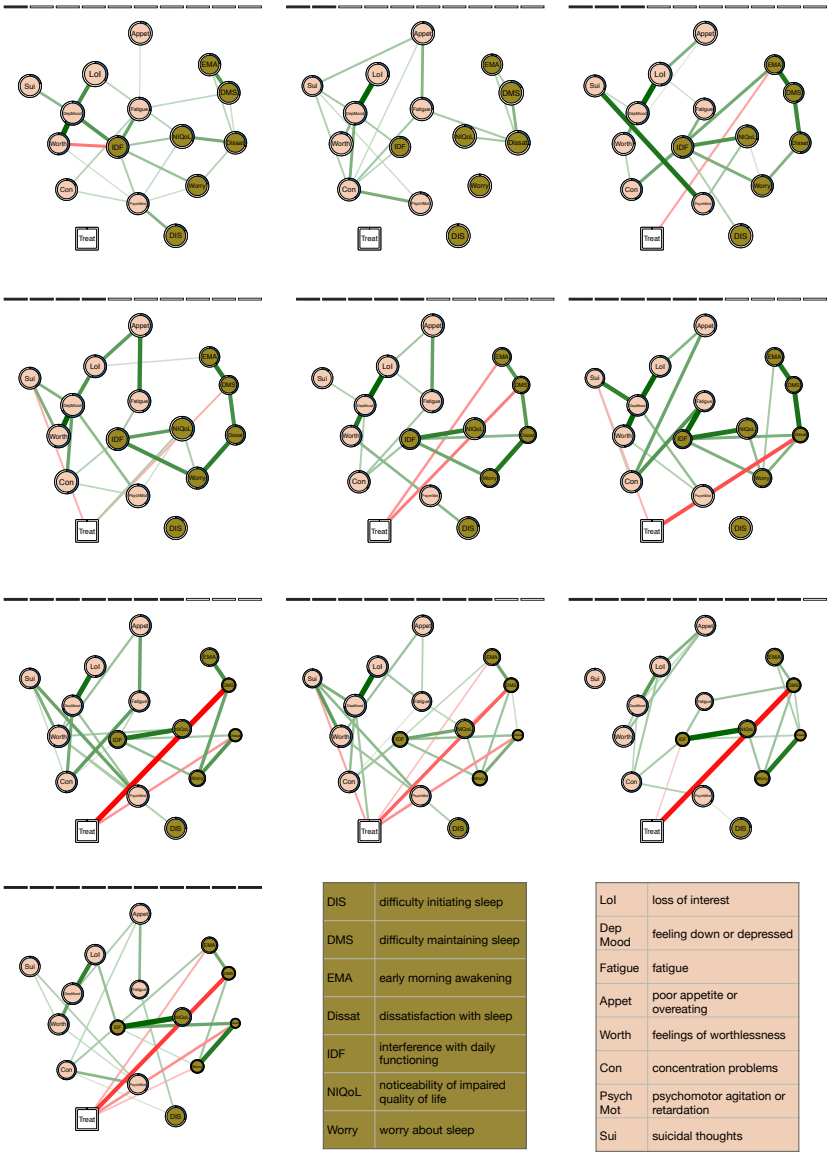
* shared first authorship

Figure 5.1 shows the sequential development of symptom-specific treatment effects throughout 10 weeks.[1] The edges visualize the unique associations between variables, controlling for their associations with all the other variables (i.e., conditional dependence relationships). Since the variable "treatment" can influence the symptom variables, but not vice versa, an edge between the treatment node and a symptom identifies the symptoms that are directly affected by treatment. The effect of treatment on each symptom relative to changes observed in controls is visualized in the size of the nodes.

First, the edges between the treatment and symptom variables revealed a direct effect of treatment primarily on insomnia symptoms. Effects commenced already after the first week of treatment and continued after completion of the intervention. The sequential development indicated that treatment first and most consistently improved the sleep problems "early morning awakening" (assessments T2, T4, T7, and T9) and "difficulty maintaining sleep" (first moderately during T2 and T3, and then increasingly so from T6 to T9). Only after 4 weeks of treatment did "dissatisfaction with sleep" improve (T5–T7 and T9), indicating a sequential effect of treatment on sleep problems first and dissatisfaction later. NIA moreover indicated that the direct effect of treatment on these specific symptoms secondarily "spread" through the network via their associations with other symptoms. For example, one of the strongest treatment effects was on "worry about sleep," even though it was directly affected by treatment on only one of the assessments (T9).

Second, NIA allowed us to observe how treatment ignited changes in the associations among the symptoms. For each symptom we inspected whether the amount of variance explained by the other symptoms (i.e., predictability) changed during treatment. The predictability systematically and robustly increased over time from, on average, 30% at baseline to, on average, 53% after assessment. There was no systematic increase or decrease in symptom variance over the course of treatment that drove the increase in predictability ($r = 0.10$). The finding suggests that treatment alters the structure of the network, which is in line with the network theory of mental disorders [7] and earlier findings [8].

1 An animated version can be found at https://github.com/tfblanken/NIA/blob/master/docs/animatedFigure.gif



DIS	difficulty initiating sleep
DMS	difficulty maintaining sleep
EMA	early morning awakening
Dissat	dissatisfaction with sleep
IDF	interference with daily functioning
NIQoL	noticeability of impaired quality of life
Worry	worry about sleep

Lol	loss of interest
Dep Mood	feeling down or depressed
Fatigue	fatigue
Appet	poor appetite or overeating
Worth	feelings of worthlessness
Con	concentration problems
Psych Mot	psychomotor agitation or retardation
Sui	suicidal thoughts

Figure 5.1

Figure 5.1: The estimated regularized networks correspond to the 10 assessment weeks (2 before treatment (T0, T1), 5 during treatment (T2–T6), 3 after treatment (T7–T9); left to right, top to bottom). The networks include the Insomnia Severity Index and Patient Health Questionnaire items (circles) and treatment (square). The edges represent the conditional dependence relations among the variables that capture the unique associations among the variables, while controlling for all the other variables in the network. Green edges represent positive associations, red edges represent negative associations, and the thickness and color saturation of the edge is proportional to the strength of the association. The size of the node is proportional to the difference in symptom severity between the treatment and control group, where smaller node sizes represent greater differences in favor of the treatment group. For each node, the proportion of explained variance by the other nodes in the network, i.e., the predictability, is visualized by a ring around each node: a completely filled ring indicates that 100% of the variance is explained, a completely empty ring corresponds to an explained variance of 0%. Treatment is directly related to "early morning awakenings" (T2, T4, T7, T9), "difficulty maintaining sleep" (T3, T4, T6–T9), "suicidal thoughts" (T3, T5), "dissatisfaction with sleep" (T5–T7, T9), "psychomotor agitation" (T7)*, or "worry about sleep" (T9). * Note that this edge is partly obscured by the edge between treatment and "dissatisfaction with sleep." However, a small edge was retrieved in the network.

We demonstrated NIA as a method to investigate the sequential process of symptom-specific direct and indirect effects of treatment. The use was illustrated by elucidating direct and indirect effects of CBTI on symptoms of insomnia and depression. Across all assessments, CBTI most strongly and directly affected specific sleep complaints. Accordingly, in the current sample of people suffering from insomnia and subclinical depression, the likely route for CBTI to improve symptoms of depression is indirect, through its effects on two dominant sleep complaints.

One previous study incorporated a treatment-allocation variable in network analysis [9], but only to determine the relative efficacy of two treatments on individual symptoms of depression in a pre-post comparison. A particular strength of the current NIA approach is that it additionally elucidates the sequential order of direct and indirect treatment-induced symptom improvements. Some limitations merit consideration. As in any multivariate approach, "directness" of effects should be interpreted cautiously if unmeasured variables are likely to be involved. Specific to our study, small treatment effects and weak associations may have gone undetected due to the moderate sample size and the use of LASSO regularization to ensure high specificity [10]. The absence of a direct edge should not be interpreted as an absence of any effect, but rather as an indication that an indirect effect is more likely given the available data. NIA can be considered as a statistical "searchlight" to identify plausible trajectories of treatment-induced effects.

NIA offers a technique to investigate the sequential development and order of treatment-induced changes of specific symptoms, highlighting likely pathways through which treatment effects evolve. Use of this technique can aid to understand treatment mechanisms and reveal clues to their optimization.

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Part III

BEYOND INSOMNIA AND DEPRESSION

6

OVERLAPPING COMMUNITIES IN PSYCHOPATHOLOGY

ABSTRACT

Network theory, as a theoretical and methodological framework, is energizing many research fields, among which clinical psychology and psychiatry. Fundamental to the network theory of psychopathology is the role of specific symptoms and their interactions. Current statistical tools, however, fail to fully capture this constitutional property. We propose community detection tools as a means to evaluate the complex network structure of psychopathology, free from its original boundaries of distinct disorders. Unique to this approach is that symptoms can belong to multiple communities. Using a large community sample and spanning a broad range of symptoms (Symptom Checklist-90-Revised), we identified 18 communities of interconnected symptoms. The differential role of symptoms within and between communities offers a framework to study the clinical concepts of comorbidity, heterogeneity and hallmark symptoms. Symptoms with many and strong connections within a community, defined as stabilizing symptoms, could be thought of as the core of a community, whereas symptoms that belong to multiple communities, defined as communicating symptoms, facilitate the communication between problem areas. We propose that defining symptoms on their stabilizing and/or communicating role within and across communities accelerates our understanding of these clinical phenomena, central to research and treatment of psychopathology.

6.1 INTRODUCTION

Ever since the nineteenth century, definitions of mental disorders were formulated and documented in classification schemes to facilitate communication about, treatment of and research on psychopathology [e.g., 1,2]. Although these classification schemes have contributed to the reliability of psychiatric classification for clinical and research purposes, diagnostic inter-rater reliability has been reported to be (very) low for some diagnostic categories [e.g., 3], suggesting that their fixed phenomenological boundaries might bypass the complex nature of mental disorders. One prominent example of this complexity is the widespread phenomenon of comorbidity - suffering from multiple mental disorders, either

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* shared first authorship

within (i.e., concurrent comorbidity) or at different periods in time (i.e., sequential comorbidity) [4]. More precisely, using current classification schemes, almost half of all people diagnosed with one disorder also meet the criteria for one or more additional disorders in their lifetime [5]. While this complexity is often treated as a nuisance, network theory offers unparalleled opportunities to lay bare the workings of complex phenomena [e.g., 6,7)]. In the present paper, we use a novel approach - *overlapping community detection* in psychopathological networks in which symptoms of various disorders interact with one another - to represent and potentially explain the complex and interconnected structure of psychopathology.

The high prevalence of comorbidity challenged the validity of the conceptualization of mental disorders as distinct entities [8] and gave rise to the *network approach* to psychopathology [9]. According to this approach, mental disorders are conceptualized as networks of interrelated symptoms (represented as nodes) that have direct connections to one another (e.g., insomnia influences fatigue: insomnia $\rightarrow$ fatigue). As such, symptoms and their connections are constitutive of a mental disorder (e.g., insomnia may cause fatigue and such relations are what constitute the disorder major depression). The network approach thereby concentrates on the evaluation of symptom-to-symptom interactions, both within as well as between disorders, with the network structure of all psychopathological symptoms representing the *landscape of psychopathology* [10]. Within the psychopathology landscape, the concept of comorbidity then follows from symptom-to-symptom interactions that cut across the 'borders' of disorders as originally defined in diagnostic classification schemes such as the DSM [11]. The rapidly expanding network approach to psychopathology appears to provide a promising framework to evaluate clinical phenomena, such as hallmark symptoms [12], heterogeneity [13], and comorbidity [9].

Fundamental to the network approach are 'bridge symptoms': specific symptoms that connect multiple disorders and thereby form possible origins of comorbidity [9,11,14]. For example, a potential bridge symptom between major depression (MD) and generalized anxiety disorder (GAD) is 'sleep problems' [e.g., 9,15]; that is, developing sleep problems may be the bridge that is crossed when someone, who already suffers from MD, develops GAD, or vice versa. Interestingly, the role of bridge symptoms within a psychopathology network corresponds to other well-studied complex observable networks. In social networks, for example, it is often observed that a network element (e.g., a person) belongs to multiple clusters (e.g., different social groups). Such 'bridge persons' are a likely route for spreading gossip due to their membership of various clusters [16]. These similar characteristics of psychopathological networks vis-á-vis other complex, observable networks pave the way for using sophisticated statistical techniques developed for these complex networks. One such technique, that will form the heart of the methodology of the present study, is community detection.

Community detection allows for evaluating large networks (e.g., social media networks, psychopathology networks) and identify communities of nodes

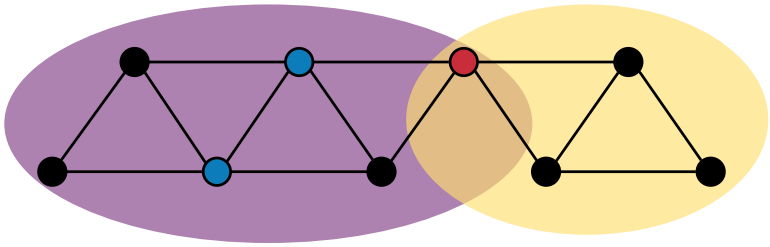


Figure 6.1: Example of a network with two problem areas: a purple community consisting of six symptoms, and a yellow community consisting of four symptoms. The blue symptoms represent potential stabilizers, while the red symptom represents a bridge symptom that facilitates possible communication between the two problem areas.

(e.g., groups of friends, groups of symptoms) [17]. One community detection algorithm that is particularly applicable to psychopathology is the Clique Percolation Method (CPM), as it allows nodes to belong to more than one community [18; applied to, for example, the human interactome, e.g., 19; social media, e.g., 20; and scientific publications, e.g., 21]. As such, this approach provides a natural representation of the theoretical stance of the network approach on the fuzzy borders between disorders [9]. Within psychopathology networks, such communities may represent specific 'problem areas'. These problem areas consist of symptoms that are closely connected to each other and tend to co-occur. The identification of these local problem areas provides novel insights into the interdependency of symptoms on the local (community) structure over and above the interdependencies in the global structure of the psychopathology network.

For example, figure 6.1 shows two problem areas (purple and yellow) that share a single symptom (red), which corresponds to the notion of *overlapping* communities. Locally, the organization of symptoms within a problem area may yield information on symptoms that *stabilize* the problem area and symptoms that *communicate* with other problem areas [22]. For example, a symptom with many connections to other symptoms in the same problem area is likely to keep, or stabilize, this problem area in a certain state, which can be either healthy or unhealthy (see blue nodes in figure 6.1). Similarly, a symptom with connections across problem areas is likely to *communicate* with other problem areas and might therefore be the origin of their co-occurrence (red node in figure 6.1). Globally, the connections between different problem areas might reveal relevant, novel information on the topology of the overall psychopathology network (e.g., which communities are connected, and how strongly?).

Based on the proposed method, we provide novel formal definitions of two core principles of the network approach to psychopathology. First, *core symptoms* of a problem area are symptoms that have many connections *within* their community and will be coined *stabilizing symptoms*. Second, *bridge symptoms* are

symptoms that have many and/or strong connections to other communities, and in some cases even belong to two or more communities, and will be referred to as *communicating symptoms*. In this paper, we show how community detection by means of the CPM method can identify different problem areas of connected symptoms and the structural organization of these problem areas.

6.2 METHODS

6.2.1 *Sample descriptives*

For the current study, we used data of a study conducted by G. A. Kerkhof and previously reported on in Kerkhof (2017) [23]. As explained in Kerkhof (2017) [23], 2089 participants were sampled from an ISO 26362-certified online research panel of Motivaction. When participants enter this panel, they sign an active consent informing them (amongst other things) that their anonymized data can be used for scientific purposes. Participants were recruited from different areas in The Netherlands and the community sample was stratified by age (ranging from 18 to 70, M=48.5, SD=14.0) and gender (49% men and 51% women). The data was collected in accordance with relevant guidelines and regulations and ethical approval was obtained by the Faculty Ethics Review Board (FMG) of the University of Amsterdam.

6.2.2 *Symptom screening*

The Symptom Checklist 90 (SCL-90-R) is a 90-item self-report symptom inventory designed to screen for a broad range of psychological problems. Participants were asked to rate all of the 90 items (see appendix D) for the last week, including today, on a five-point Likert scale of distress, ranging from not at all (1) to extremely (5). The items can be combined into eight symptom scales: Depression, Anxiety, Agoraphobia, Sleep difficulty, Somatization, Interpersonal sensitivity, Acting-out hostility, and Cognitive-performance deficits. These scales, plus nine unscaled items, can be combined into a total score ranging from 90 to 450, with higher scores indicating more severe symptom levels. The SCL-90-R scores in the current study sample ranged from 90 to 384 (M=124.8, SD=41.8), and 33% of the participants (N=695) scored above the norm score of 123.

6.2.3 *Statistical analyses*

NETWORK ESTIMATION We estimated a sparse Gaussian network based on the polychoric correlations between the responses to the SCL-90-R items using the glasso-method implemented in the R-package *qgraph* [24]. Glasso estimates partial correlations between each pair of variables conditioning on all other variables. As such, we can interpret the network as depicting conditional

dependence relations: an edge between two symptoms A and B indicates that these symptoms are conditionally dependent, given all other symptoms in the network. To decrease the number of spurious partial correlations, Glasso uses the regularization technique Least Absolute Shrinking and Selection Operator (LASSO; [25]). The LASSO technique utilizes a tuning parameter that controls the sparsity of the estimated network by pushing small edge weights (i.e., polychoric correlations) to zero. The Extended Bayesian Information Criterion (EBIC; [26,27]) is then used to select the best fitting regression function. To check the robustness of the estimated network we performed additional network stability checks using the R-package *bootnet* [28] and appended the results as supplementary material, see appendix D.

CLIQUE PERCOLATION METHOD The CPM algorithm aims to find percolation clusters (communities) using the notion of k-cliques: complete subgraphs of k nodes (i.e., a fully connected subgraph of k nodes). Two cliques are adjacent when they share all but one (k-1) nodes. A k-clique percolation cluster is then defined by "the maximal set of k-cliques that can be reached from each other via a set of k-clique adjacency connections" [29]. The CPM algorithm has been extended to incorporate edge weights in identifying the communities. This algorithm, called the Clique Percolation Method with weights (CPMw), includes a k-clique into a community when its intensity I exceeds a fixed threshold [29]. The intensity of a k-clique is the geometric mean of the edge weights. Thus, a community according to the CPMw algorithm is the maximal set of k-cliques that are k-clique adjacent and have intensities above the threshold. Hence, the communities are dependent on the number of nodes k in a clique and the intensity threshold I.

The CPM algorithm is implemented in the program CFinder [30]. Using the edge list of the Gaussian graphical model estimated on the SCL-90-R data, we determined, for each k, the optimal intensity threshold I to obtain the richest community structure. Specifically, starting with an intensity threshold equal to the largest edge weight, and then lowering I to the point that a giant cluster emerges is called the percolation transition. The richest community structure is found at values of I just above this transition. In this way, the threshold is high enough to prevent a giant cluster that would obscure the details of smaller communities, and low enough to prevent a large number of separate k-cliques [29].

For each fixed k (i.e., k = 3, 4, 5, 6), we determined the optimal threshold according to these principles [29] by (i) lowering the intensity threshold, first set equal to the largest edge weight, by steps of .1 until cliques of size k emerged; (ii) then we further lowered I by smaller steps of .01 until a giant cluster emerged, i.e., the percolation transition. Subsequently, (iii) we increased I by steps of .001 to find the values for I just above the percolation transition. After the identification of the optimal I value for each k separately, we compared the k parameters in terms of the broadness of their community size distribution at their optimal I.

The initial intensity threshold was set equal to the largest edge weight of .48. The optimal threshold for k = 3, 4, 5, 6 was equal to .099, .0695, .044, and .01, respectively. We then chose k = 3 as it had the broadest community structure, i.e., communities of different sizes.

LOCAL STRUCTURE ANALYSIS To investigate the local structure of the communities, we analyzed the edge weights of connections nodes have within and between their communities. For the detection of stabilizing nodes, we summed the absolute edge weight values a given node has within its community (stabilizing index). For the detection of communicating nodes, we summed the strength of connections a given node has between its communities (communicating index). Notably, these indices are based on commonly used centrality measures in the network literature [31] usually applied to evaluate the role of symptoms on the global level (i.e., the network as a whole). However, when one assumes that there are meaningful sub-structures within a network on a local level, using centrality measures at the global level does not suffice to identify the symptoms that play an important role at these local levels. Thus, while these metrics are essentially the same, they are applied at different levels. Note that this could imply that symptoms ranking highest on global centrality (taking into account all symptoms at once) might not be the same as the symptoms that rank highest on local centrality (taking only symptoms in the local sub-structure into account).

6.3 RESULTS

6.3.1 *Global community structure*

Based on the *clique-percolation* method, 18 communities were identified in the psychopathology network, with the size of the communities ranging from three to 39 nodes. Appendix D contains a tabulated representation of all communities and their symptoms, ordered by the original SCL-90-R dimensions. Note that we use the SCL-90-R dimension labels whenever we refer to the originally proposed dimensions. Figure 6.2 shows how strongly these communities are connected via shared symptoms. We labelled the communities (or: problem areas) according to a summary of the most central symptom, i.e., the symptom with the strongest connections to other symptoms within the respective community (e.g., the first community was labelled Nervousness according to its most central symptom *nervousness or shakiness inside*). Communities are further denoted by their number (#community number) and symptoms are referred to by the item order in the SCL-90-R (item number). Every community overlapped with at least one other community. The CPM method identified strongest overlap between the following communities: *Low in Energy* (community #2) and *Panic* (#9) share six symptoms, *Low in Energy* (#2) and *Self-conscious* (#13) share

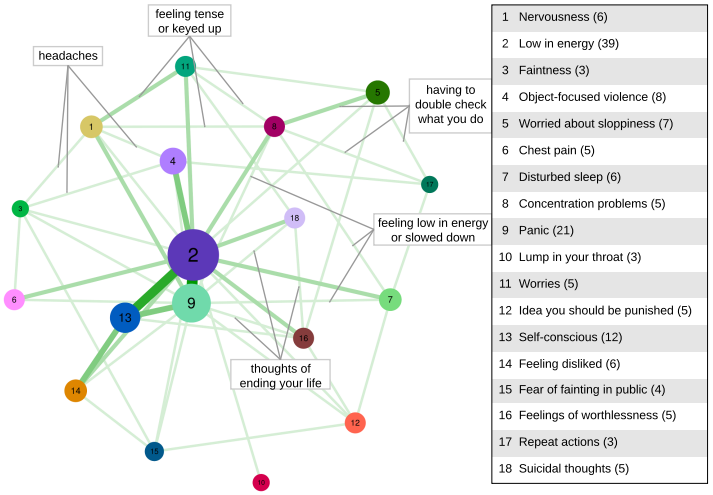


Figure 6.2: Nodes represent communities and edges correspond to number of symptoms shared, with thicker edges corresponding to more bridge symptoms. Each community is labelled according to its most central (i.e., stabilizing) symptom and its size (i.e., number of symptoms) is depicted between brackets (see legend). The five symptoms depicted in grey boxes are examples of how communities are connected through bridge symptoms.

five symptoms and *Self-conscious* (#13) shares three symptoms with both *Panic* (#9) and *Feeling disliked* (#14).

Generally, when comparing the resulting community structure (as depicted in figure 6.2) to the SCL-90-R dimensions, a few distinctive global features deserve mention. First of all, while two communities (#3 and #14) consist of symptoms from only a single SCL-90-R dimension, none of them covers all symptoms of a specific dimension. For example, the third community (Faintness) consists of merely three symptoms from the Somatization dimension (headaches, faintness or dizziness, and nausea or upset stomach). Second, most communities consist of symptoms from two or more different SCL-90-R dimensions. Although these communities comprise symptoms from originally different dimensions, there seems to be a shared common theme in each community. For example, although the first community (Nervousness) covers symptoms from three different SCL-90-R dimensions (Depression, Anxiety, Somatization), all symptoms are related to feeling tense or nervous.

6.3.2 *Local community structure*

The legend of figure 6.2 lists the 18 communities, labelled according to the symptom that ranked highest on the stabilizing index. These symptoms can thus be expected to have a high impact on nodes within their community or that are most influenced by their community members. For example, item 2 nervousness

or shakiness inside has the highest stabilizing index in community #1, which consists of symptoms related to feeling tense or nervous. This indicates that feeling nervous or shaky might determine to a large extent whether or not a person also shows several other related symptoms within this community.

In table 6.1 we depict the symptoms ranking highest on the communicating index. These symptoms can be expected to play an important role in connecting different problem areas and are thus indicative of bridge symptoms. For example, the symptom headaches seems to play an important role in connecting symptoms between the *Nervousness* (#1), *Low in Energy* (#2), *Faintness* (#3), and *Object-focused Violence* (#4) communities. This suggests that symptom activation across these connected problem areas might be predicted by monitoring headaches.

Note that there are three symptoms that rank high both as communicators and stabilizers (see table 6.1). For example, the symptom feeling low in energy or slowed down ranked among the highest communicators and stabilizes one of its communities. These symptoms might flag the most decisive symptoms, since they stabilize their community and at the same time communicate with symptoms of other communities. Some overlap between stabilizing and communicating symptoms is hardly surprising, as both these measures depend on the strength and number of connections a symptom has. Yet, as can be seen in table 6.1 this overlap is sufficiently low to treat stabilizing and communicating symptoms as different constructs.

6.4 ILLUSTRATION

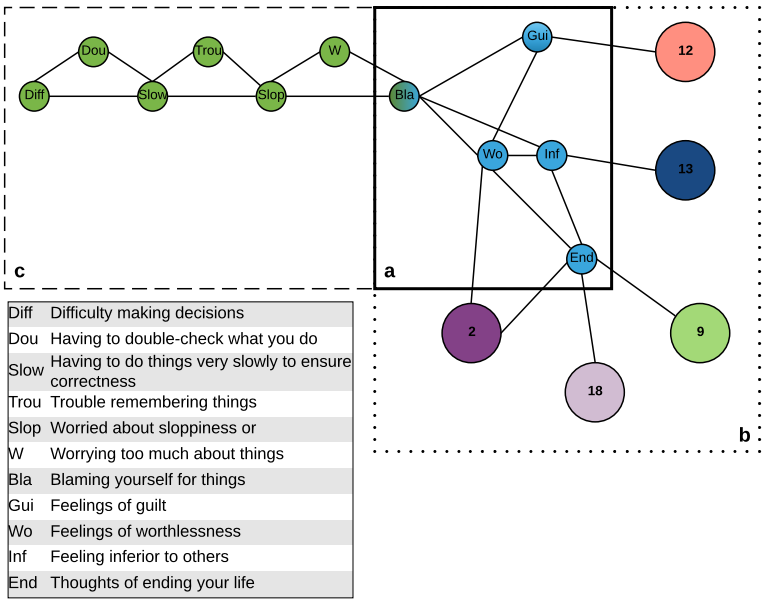
Inspecting the local structure offers additional information both on the relations within a community as well as on the communication between communities via so-called *communicating nodes* (i.e., symptoms that have many and/or strong connections to other problem areas). To illustrate this, we focused on the structure of the 5-symptom *Feelings of Worthlessness community* (#16) with mainly symptoms from the depression dimension. This detailed focus has implications for the concept of hallmark symptoms and the study of heterogeneity within this problem area, and also for its comorbidity with other problem areas.

First, the stabilizing index of the symptoms in this community reveals what might be its core symptom: *feelings of worthlessness* (item 79) is connected to all other symptoms, i.e., it has a direct connection to *blaming yourself for things*, *feelings of guilt*, *feeling inferior to others* and *thoughts of ending your life* (see figure 6.3a). Second, the communicating symptoms of this problem area and their connections to adjacent problem areas, also consisting of symptoms from the depression dimension, reveal possible pathways for the clinical heterogeneity of depression. Figure 6.3b shows that five additional communities are connected to the *Feelings of Worthlessness* community. For example, the bridge depression symptom *thoughts of ending your life* (item 15) funnels a direct connection to a 5-symptom problem area related to hopelessness (*Suicidal thoughts* #18),

Table 6.1: Strongest communicators that belong to three or more communities.

Symptom (item number)	Communities (# community number)
Headaches (1)	Nervousness (#1), Low in energy (#2), Faintness (#3), Object-focused violence (#4)
Feeling low in energy or slowed down (14)*	Low in energy (#2), Disturbed sleep (#7), Concentration problems (#8), Panic (#9)
Thoughts of ending your life (15)*	Low in energy (#2), Panic (#9), Feelings of worthlessness (#16), Suicidal thoughts (#18)
Hearing voices that other people don't hear (16)	Low in energy (#2), Object-focused violence (#4), Panic (#9)
Having to double-check what you do (45)	Worried about sloppiness (#5), Concentration problems (#8), Repeat actions (#17)
Feeling hopeless about the future (54)	Low in energy (#2), Worries (#11), Suicidal thoughts (#18)
Feeling tensed or keyed up (57)	Nervousness (#1), Concentration problems (#8), Worries (#11)
Feeling uneasy when people are watching or talking about you (61)	Panic (#9), Self-conscious (#13), Feeling disliked (#14)
Feeling afraid you will faint in public (82)*	Low in energy (#2), Panic (#9), Fear of fainting in public (#15)

* These symptoms are also stabilizers.



Diff	Difficulty making decisions
Dou	Having to double-check what you do
Slow	Having to do things very slowly to ensure correctness
Trou	Trouble remembering things
Slop	Worried about sloppiness or
W	Worrying too much about things
Bla	Blaming yourself for things
Gui	Feelings of guilt
Wo	Feelings of worthlessness
Inf	Feeling inferior to others
End	Thoughts of ending your life

Figure 6.3: Illustration of (a) the local structure of Feelings of Worthlessness community (#16), (b) its connection to other communities; and (c) a symptom-level example of its connection to the community Worried about Sloppiness (#5).

such as thoughts of death and dying and feeling hopeless about the future. Similarly, *feeling inferior to others* (item 41) connects the problem area to another problem area of symptoms on interpersonal sensitivity (Self-conscious #13), e.g., *feeling very self-conscious with others* (item 69). Third, the local structure shown in figure 6.3c suggests that the shared symptom of *blaming yourself for things* (item 26) connects depression symptoms (*Feelings of Worthlessness*, #16) to cognitive performance deficits (*Worried about Sloppiness*, #5). The above presented inspection of the local structure indicates that similar symptoms indeed tend to cluster together and simultaneously points us towards the specific symptoms that funnel the interdependency of problem areas.

6.5 DISCUSSION

In current classification schemes, psychological disorders are defined as distinct entities characterized by hallmark symptoms. In this paper, we evaluated the structure of psychopathology without the theoretical boundaries of these classification schemes, as such allowing for the complex and multi-faceted structure of psychopathology. Specifically, we took a data-driven approach using community detection techniques to study the co-occurrence of symptoms and detect possible problem areas, i.e., communities of closely related symptoms. As such, these problem areas are empirically derived and not theoretically defined.

We applied community detection to a large psychopathological symptom network and identified 18 problem areas. Using these problem areas, we evaluated three complex clinical phenomena that are crucial to our understanding of the development, prevention and treatment of mental disorders: hallmark symptoms, heterogeneity and comorbidity. The results of the current study illustrate how the identified problem areas capture important information on all three phenomena by focusing on the differential role of symptoms within a problem area: *stabilizing* symptoms and *communicating* symptoms. For example, symptoms of the depression dimension decompose into different problem areas. While it is not our objective to rephrase the nosological definition of depression, the problem areas do inform us on what depression symptoms are likely to stabilise smaller problem areas (core symptoms), are more likely to co-occur than others (heterogeneity), or are likely to co-occur with symptoms from other disorders (comorbidity). There are a few promising avenues following from this focus.

First, stabilizing symptoms show many and/or strong connections to other symptoms in the same problem area and could be thought of as the core symptoms of one such problem area. An important next step would be to evaluate whether these symptoms are indeed more prevalent in the designated problem areas. For example, in a problem area consisting predominantly of depression symptoms, *feelings of worthlessness* was a stabilizing symptom. This suggests that this particular symptom is at the core in at least some form of "depression", implying that for some individuals this symptom may play

an important role in triggering and/or maintaining their depression. The importance of this particular symptom is theoretically substantiated in the revised learned helplessness model of depression [32]. While some research based on this model concludes that feelings of worthlessness define one's vulnerability to develop depression [e.g., 33], others show that depression samples vary in the reported frequency of this symptom suggesting that it might not be a hallmark symptom [34]. Interestingly, such apparent inconsistencies align with our results: feelings of worthlessness might play a stabilizing role in one, but not all, problem areas that consist of depression symptoms in the reported psychopathology network. It should be investigated whether this symptom indeed has a perpetuating function within the individual network *over time* in people suffering from this constellation of depression symptoms.

Second, communicating symptoms can potentially generate a better understanding of both heterogeneity and comorbidity. Communicating symptoms have many and/or strong connections to other problem areas and, as such, facilitate the communication between problem areas. In the case where two problem areas consist (predominantly) of symptoms that belong to a single disorder as defined in current nosologies, these communicating symptoms relate to the phenomenon of heterogeneity. For example, the peripheral symptom *thoughts of ending your life* bridged two depression-like communities: one characterized by worthlessness and the other characterized by hopelessness. The finding that these symptoms cluster in different depression-like communities points us towards possible patterns of heterogeneity within depression. Depression, as defined by the DSM-V, has shown to be a highly heterogeneous disorder with many different symptom patterns [35]. It would be valuable to assess whether the different depression-like communities correspond to different, clinically observed, symptom patterns. Although the communities identified at a group level cannot be readily extrapolated to the individual level, these symptom patterns, after cross-validation, might offer new leads on what specific symptoms can be identified as a risk factor for infecting a (neighbouring) set of comorbid problems. For example, if an individual suffers mainly from depression symptoms within the Worries (#11) problem area, this individual might be more likely to develop symptoms of the directly related Nervousness problem area (#1; consisting predominantly of symptoms from the anxiety dimension). Conversely, an individual who suffers from depression symptoms in the Feelings of Worthlessness (#16) problem area might have a higher risk to develop or suffer from symptoms of the problem area Idea You Should Be Punished (#12; mostly symptoms on intrusive thoughts).

Alternatively, in the case when the two problem areas consist of symptoms that belong to multiple, supposedly distinct disorders, the communicating symptoms relate to comorbidity. For example, the symptom *blaming yourself for things* belonged to a depression-like problem area characterized by worthlessness and a problem area characterized by cognitive performance deficits. In this particular example, we would hypothesize that *blaming yourself for things* plays a crucial role in patients suffering from not only depression symptoms but also

cognitive performance deficit symptoms. It would be important to evaluate whether the identified bridge symptoms indeed play an important role in the co-occurrence of problem areas or disorders in clinical populations. Thus, when adhering to current classification schemes heterogeneity and comorbidity are distinct concepts, while the current framework suggests that they result from the same core principle of communicating symptoms.

Third, we should not limit the investigation of these structures to cross-sectional symptom networks. The study of intra-individual changes in communities of symptoms can point us towards *growth* (i.e., symptoms joining the problem area) or *contraction* (i.e., symptoms leaving the problem area) patterns of specific problem areas that might offer novel starting points for intervention and treatment. Relatedly, these developmental patterns of problem areas could be key to understanding intra-individual characteristics in psychiatry, such as vulnerability and resilience [11,35]. Here, the role of bridge symptoms is crucial: the number and strength of connections of a symptom in one problem area to another problem area increases the probability of this symptom joining the clinical profile of an individual.

6.5.1 *Limitations*

A few limitations deserve mention. First, in the current report we studied potential pathways in the landscape of psychopathology in a community sample as we did not aim to draw conclusions about DSM-5 diagnoses. We argue, however, that the results of the current study provide first insights into the structure of the landscape of psychopathology and its constructs in a non-clinical sample. Future investigations should apply this approach to a clinical sample to validate these pathways for clinical populations. Second, while we mostly treated stabilizing and communicating aspects of symptoms as two distinct roles, our results indicated that there is some overlap between stabilizing and communicating symptoms. Future research should focus on further disentangling stabilizing and communicating symptoms and whether overlap between these measures is a relevant finding of its own (e.g., that symptoms ranking high on both measures might be the most decisive symptoms to suffer from). Finally, it should be noted that the identified communities depend on (i) the community detection algorithm, and within the chosen algorithm (CPM), on (ii) the stability of the input network and (iii) the chosen parameters for the clique size k and the intensity threshold I. First, given our goal to further study the complex and sometimes partly overlapping structure of psychopathology, the possibility for a node to belong to multiple communities at once (i.e., overlapping communities), and the absence of strong assumptions about the size and form of local substructures was dominant in selecting an algorithm and resulted in our choice for CPM. Second, to ascertain robustness of the identified communities based on the input network, we assessed the stability of the estimated network. The input network was stable in terms of the

strength and number of connections a node has, which is particularly important for the CPM in identifying communities. Third, to select the parameters k and I, we followed the proposed guidelines of Farkas et al. (2007) [29] to obtain the richest community structure possible. It is important to note that different communities can be found by changing these parameters. While this can be considered a limitation of the approach, we also believe that this can be a tool to inspect different properties of the psychopathology landscape. For example, by increasing the minimal clique size, one would obtain larger communities and thereby possibly gain more insight into the larger, global structure of psychopathology. Similarly, by increasing the intensity threshold, fewer but more strongly connected communities will be derived. If one aims to inspect the local structure on a more detailed level, lowering the intensity threshold will reveal more, and larger communities. Taking these things into account, we do not propose that problem areas should be interpreted as existing entities. Rather, we argue that applying these techniques can reveal substructures at different levels of symptom networks and allow us to relate them to the role of individual symptoms.

6.5.2 *Concluding remarks*

The identification of stabilizing symptoms comes with great promise, as its state is informative with respect to the state of the other symptoms in its problem area. For example, our results suggest that people with strong feelings of worthlessness are likely to blame themselves for things and experience feelings of guilt (and vice versa). Because of its many strong connections, one is intuitively inclined to interpret the stabilizing symptom *feelings of worthlessness* as a target for intervention programs. The potential success of such an intervention is, however, strongly dependent on the specific nature of the symptom itself (i.e., the symptom itself must be responsive to treatment; [37]) and the temporal order of activation in relation to its neighbours (i.e., the symptom must be a cause rather than an effect of its neighbours). Thus, the viability of treating a stabilizing symptom must ultimately be determined longitudinally. Nevertheless, the identification of stabilizing symptoms in cross-sectional data does point us towards potential hubs of the psychopathological system that funnel more symptom activation (either as cause or effect) within a local structure than others.

In sum, the network approach to psychopathology has paved the way for novel techniques to study the interdependency of symptoms as a complex network. To date, however, it was not possible to accommodate the idea of bridge symptoms that connect multiple problem areas. The present study is the first to apply overlapping community detection to psychopathology and conclude that the identification of overlapping communities of symptoms points us towards novel research lines into possible pathways between and within problem areas in psychopathology. In addition, the present study has complemented the

network analysis toolbox of clinical psychology and psychiatry by providing novel definitions of communicating and stabilizing roles of symptoms in the psychological landscape.

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7

ADHD COMMUNITIES

ABSTRACT

Pediatric Attention Deficit / Hyperactivity Disorder (ADHD) is a heterogeneous condition. In particular, children with ADHD display varying profiles of dispositional traits, as assessed through temperament and personality questionnaires. Data-driven community detection analyses based on temperament dimensions identified an irritable profile of patients with ADHD, uniquely characterized by elevated emotional dysregulation symptoms. Belonging to this profile increased the risk of developing comorbid disorders. Here, we investigated whether we could replicate this profile in a sample of 178 children with ADHD, using community detection based on personality dimensions. Stability of the identified profiles, of individual classifications, and clinical prediction were longitudinally assessed over a one-year interval. Three personality profiles were detected: one with higher ADHD severity and lower levels of openness to experience (profile 1; N=38), one with lower levels of agreeableness (profile 2; N=73), and one with lower levels of neuroticism (profile 3; N=67). The identified profiles did not replicate the original temperament-based profiles. In particular, no profile matched the previously reported irritable profile. Nonetheless, despite changes in individual classifications, the profiles themselves were highly stable over time and of clinical predictive value. Specifically, profile-membership at baseline predicted the effect of medication at follow-up over and above initial ADHD symptom severity. Whereas children belonging to profiles 1 and 2 benefited from starting medication, children in profile 3 did not. This finding suggests that personality profiles could play a role in predicting treatment response in ADHD.

7.1 INTRODUCTION

Heterogeneity in psychiatric disorders as defined by current nosologies such as the DSM-5 is ubiquitous. Most disorders can indicate multiple, only partially overlapping, symptom profiles that are likely to result from multiple independent mechanistic pathways [1–6]. A prominent example is Attention Deficit / Hyperactivity Disorder (ADHD), a diagnosis associated with multiple risk factors (3), a range of comorbidities [7], and various impairments

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[8,9]. Heterogeneity in ADHD is evident across multiple levels: from genetics [10] to neural systems [11,12], cognition [13–15] and clinical course [15]. This multi-level heterogeneity has hampered the quest for neurobiological markers [11] and the optimization of treatment. Finding meaningful ways to address heterogeneity when assessing etiological factors, neurobiological profiles, and clinical outcomes is therefore crucial.

In current nosologies ADHD is defined as a neurodevelopmental syndrome with two main symptom domains of inattentive and hyperactive/impulsive symptoms [16]. Next to these core symptoms, ADHD is consistently associated with dispositional traits, i.e., stable individual differences in human behaviour as assessed through temperament and personality questionnaires [17,18]. Specifically, children with ADHD are on average lower in conscientiousness or effortful control, reactive control, and agreeableness, and higher on neuroticism or negative emotionality, when compared with typically developing children [19,20]. At the same time, children with ADHD show differential patterns in these dispositional traits that are potentially clinically relevant [21]. Using clustering techniques to uncover different profiles of dispositional traits might therefore offer a promising approach to uncover within-diagnosis profiles that potentially have unique clinical predictive value [22].

In a pioneering study on heterogeneity in ADHD, Karalunas et al. (2014) used community detection [23] on dispositional traits (i.e., temperament scores) to detect biologically informed profiles [12]. Three novel data-driven temperament profiles were identified within ADHD, which were labelled mild, surgent and irritable; each associated with distinct neurobiological correlates. The three profiles were replicated in an independent sample, and the irritable profile was shown to be the most stable over time, as 61% of irritable children were consistently assigned to the same profile across all three years of follow up [24]. Importantly, in a combined model including initial ADHD presentation (i.e., predominantly inattentive, predominantly hyperactive/impulsive, or combined) and Oppositional Defiant Disorder (ODD) diagnosis, only the identified temperament profiles were found to predict the onset of new disorders. Crucially, the irritable profile consisted of children both with and without comorbid diagnoses, and 65% of the children that belonged to this group were free of any comorbid diagnosis, including ODD or Disruptive mood dysregulation Disorder (DMDD). This stresses the unique clinical relevance of the temperament profiles, when compared with existing diagnoses and subtypes.

Because of the high stability and unique clinical predictive value, this irritable profile is of particular interest. Irritability designates a proneness to anger that is inconsistent with an individual's developmental level [25] and is best described by two components: tonic and phasic. The tonic component refers to a persistent angry, grumpy, or grouchy mood, whereas the phasic component refers to behavioural outbursts of intense anger [26]. Although irritability is not a defining diagnostic feature, impairments in irritability are highly prevalent in childhood ADHD and affect at least half of patients in clinical samples [27–29].

Irritability is also strongly associated to defiant behaviours [30], and as such defined as a dimension of ODD in the DSM-5 [16].

Next to increased levels of anger, the irritable profile identified by Karalunas et al. (2014, 2918) was also characterized by broader emotional dysregulation (ED) manifestations such as discomfort, fear, and sadness. The finding that the irritable profile predicted new onset of comorbid disorders (primarily in the form of new anxiety disorders) in patients with ADHD is in line with available data, showing that the irritable dimension of ODD is a significant predictor of depression and anxiety disorders [31]. In clinical practice, investigating whether a child belongs to the irritable profile may therefore help to identify a subgroup of patients with ADHD with sub-diagnostic ED manifestations who are at increased risk of developing emotional comorbidities, which opens up new possibilities for early detection and prevention.

For the identified irritable profile to fulfil this potential, reproducibility across samples is essential. Karalunas et al. (2018) replicated their initial findings in a new sample, but both samples were collected within the Oregon ADHD Program in the United States. Whether the three profiles, and in particular the irritable profile are also found in other cultural areas remains to establish. Furthermore, dispositional traits were exclusively assessed using the Temperament in Middle Childhood Questionnaire (TMCQ) – a theory-driven questionnaire based on Rothbart's temperament model [32]. Yet, it should be noted that the best way to conceptualize dispositional traits in children remains a matter of disagreement in the field, and multiple trait-based personality and temperament models coexist [22].

Historically, temperament and personality traits were studied separately. Compared to personality traits, temperament was thought to capture traits that have a stronger genetic or neurobiological basis [33]. In Rothbart's model, the trait structure is summarized in three broad, well-validated domains: (a) negative affect, encompassing emotions such as fear, sadness, and anger/frustration; (b) positive affect (or surgency), reflecting tendency to express excitement and happiness, willingness to approach novel stimuli, and overall activity level; and (c) effortful control, describing top down self-regulatory capacities and tendencies [33].

Despite the initial coexistence of these two separate lines of research, several scholars made a compelling case that temperament and personality systems describing children's and adolescent's traits can be considered to be "more alike than different", and are actually tapping into overlapping trait domains in somewhat different fashions [34–37]. In this context, the most common personality model, the Five Factor Model (FFM), has been described as a useful unifying framework [35]. Previous research indeed suggests that the dimensions of neuroticism (predisposed to emotional distress vs. emotionally stable), extraversion (energic and thrill-seeking vs. sober and solitary), and conscientiousness (disciplined and fastidious vs. laid-back and careless) represent the three higher order domains of negative affect, positive affect, and effortful control found in the Rothbart's temperament model [35]. In addition, the FFM

assesses the dimensions of agreeableness (kind and trusting vs. competitive and arrogant) and openness-to-Experience (curious and unconventional vs. traditional and pragmatic), two traits that are not represented at the higher order in the temperament framework [35].

It remains currently unclear whether different measurement instruments affiliated to different temperament or personality models will yield overlapping community profiles, or whether each instrument or model may provide different but complementary valuable information. Notably, two previous studies have used personality questionnaires with a clustering approach to identify ADHD profiles, one in young children (3-6 years old) with ADHD [38], and the other in a large sample of children and adolescents (6-18 years old) with ADHD and healthy controls [22]. In this second study, latent profile analysis was conducted on the Big-Five factors, and three main profiles of patients with ADHD emerged: a group characterized by low extraversion, a group with high extraversion, and a more disturbed group with low control and of whom nearly all members displayed a comorbidity, either in the form of a disruptive behaviour disorder, or anxiety/mood disorder. Although some similarities between these profiles and those identified by Karalunas et al. can be found, they cannot be easily matched. For example, high neuroticism or negative emotionality was not specific to one but two profiles, and this was not the dimension along which the profiles differed the most. These results suggest that despite potentially tapping into the same construct, temperament and personality questionnaires may contribute to identify different profiles in children and adolescents with ADHD, possibly yielding each unique predictive value. Another possibility for failing to replicate the ADHD profiles across dispositional frameworks might be that both samples differ in age range (7-to-11 years vs. 6-to-18 years). Age-related effects on temperament and personality have indeed been solidly established during childhood and adolescence [35,39].

In the present study, we investigated whether the profiles identified by Karalunas et al. (2014, 2018) are robust across dispositional traits by examining their replicability in a new sample of children with ADHD with a similar age range, using a different measure of dispositional traits (i.e., a personality questionnaire). A sample of children with combined-type ADHD was recruited, and assessed at two time points with a one-year interval. This approach allowed us to concurrently investigate the temporal stability of both of the profiles and the classification of individuals. Children were assessed with the Big-Five Questionnaire for Children (BFQ-C), a tool instantiating the FFM, with an empirically well-established five factor structure [40–43]. Measures of clinical severity were also obtained, and the predictive value of the profiles identified at T0 with regard to severity at T1 was investigated. Profiles that were based on all five personality factors were compared to the profiles identified using only the three personality factors that overlap with the temperament model (i.e., neuroticism, extraversion and conscientiousness). In both cases, our hypothesis was that the neuroticism items of the FFM would drive the detection of a subgroup of

children with ADHD characterized by unique increases in irritability, and that this subgroup would be the most stable over time.

7.2 METHODS

7.2.1 *Recruitment procedure*

221 French-speaking families living in France or Belgium participated in this study. The research was approved by the Ethics Committee of the ULB-Erasme Hospital, Brussels, Belgium (P2016/124) and therefore conducted in accordance with the latest version of the Declaration of Helsinki. Families were recruited through a network of clinicians (52% of final cases), and by advertising through the Belgian and French national ADHD associations who advertised this research project on their social network webpages (48%). Child psychiatrists, pediatricians and child psychologists belonging to an informal network of ADHD researchers affiliated to the French-Speaking ADHD International Congress were contacted by the last author to assist with recruitment. Clinicians introduced the research design to parents and provided them with a booklet describing the project along with contact information. Families volunteered through emails, and were contacted by the research team through telephone to assess eligibility. Children had to be 6-to-11 years old, to have been diagnosed with ADHD, and to be medication-naive at the time of recruitment. Parents were each invited to fill in the questionnaires online, while being informed that one informant was sufficient to participate in the study. A phone interview was scheduled with one parent to collect demographic information and to conduct a diagnostic interview. One year after the initial (T0) phone interview, parents were contacted by email and provided with codes for follow-up assessment (T1). At each time point, access to the interface was preceded by an information statement and conditioned to the validation of an electronic consent form.

7.2.2 *Diagnostic procedure and exclusion process*

After eligibility assessment, one parent completed a semi-structured clinical interview (Kiddie Schedule for Affective Disorders and Schizophrenia for School Aged Children-Present and Lifetime Version (K-SADS-PL); [44]) administered during a phone call by a doctorate-level clinical psychologist [TV] with a ten-year practice experience in child psychiatry. Participants were excluded if they failed to meet the diagnostic criteria for combined-type ADHD based on the K-SADS-PL; were prescribed psychotropic medications, had neurological impairment, seizure history, other major medical conditions, prior diagnosis of intellectual disability, autism spectrum disorder (ASD), or psychosis. Participants were further excluded if their score at the ADHD Rating Scale IV (ADHD-RS-IV) total scale was below the 93th percentile for their age group [45]. Of the 221 families that were approached initially, 43 were excluded: 20

failed to complete all questionnaires at T0; 16 children were excluded based on the clinical interview, which revealed insufficient symptom numbers or clinical severity, or a non-combined form of ADHD; 4 children were excluded due the presence of comorbid ASD; finally, 3 participants were excluded based on their ADHD-RS Total scores. The final sample at the first time point (T0) therefore consisted of 178 combined-type ADHD cases. Demographic characteristics of the sample are reported in table 7.1. At T1, 12 families failed to complete the second wave of questionnaires, yielding a follow-up sample of 166 cases (attrition rate: 6.7%).

Table 7.1: Descriptive information and longitudinal outcomes for the complete sample

Characteristics	**T0**	**T1**
Basic demographics		
N	178	166
Boys:Girls	135:43	126:40
Age mean (±SD) years	8.2 (1.4)	9.2 (1.4)
N(%) on stimulant medication	0 (0)	74 (44.6)
Comorbidity (%)		
GAD	16.9	
Specific phobia	4.5	
SAD	2.8	
Social phobia	1.1	
Enuresia	2.8	
Encopresia	1.1	
Tic disorder	5.1	
ODD	5.6	
DMDD	13.5	
ADHD and severity measures mean (±SD)		
ADHD-RS total score	41.20 (6.76)	36.05 (9.32)
ADHD-RS inattentive score	20.61 (4.11)	18.21 (4.91)
ADHD-RS hyp/imp score	20.59 (4.22)	17.84 (5.52)
SDQ impact score	6.01 (2.59)	5.11 (2.77)

Note. GAD = Generalised Anxiety Disorder; SAD = Separation Anxiety Disorder; ODD = Oppositional Defiant Disorder; DMDD = Disruptive Mood Dysregulation Disorder; ADHD-RS = Attention-Deficit with Hyperactivity Rating Scale IV; SDQ= Strengths & Difficulties Questionnaire; T0 = Time 0; T1 = Time 1.

7.2.3 *Assessment of personality and clinical outcomes*

At least one parent of each child completed the Big-Five Questionnaire for Children (BFQ-C) at each time point [40] (French adaptation: [43]). The BFQ-C is based on the FFM, and contains a total of 65 items, with five scales of 13 items. At T0, double informant data (i.e., -mother and –father data) were available for 15 (8,4%) of the initial 178 children participating. For these cases, scores were averaged across informants at the item level prior to any reported analysis.[1] For single informant data, the same informant completed the questionnaire at both time points. Scale reliabilities were assessed at T0, yielding the following (Cronbach's alpha) scale reliabilities: 0.71 for extraversion, 0.85 for agreeableness, 0.81 for conscientiousness, 0.83 for neuroticism, and 0.84 for openness.

Clinical outcome was evaluated using scores of parent-rated functional impairment on the Impact Supplement of the Strengths and Difficulties Questionnaire (SDQ) for age 4-17. Items on overall distress and impairment were summed to generate an impact score ranging from 0 to 10, with higher scores indicating greater impact [46,47].

7.2.4 *Statistical analysis*

To identify communities, we followed the same procedures as Karalunas et al. (2014; 2018).

DATA PREPARATION We first standardized the 65 items of the BFQ-C to the sample mean and standard deviation, after which we computed the child-by-child profile correlations.

COMMUNITY DETECTION We applied the weight conserving modularity algorithm to the child-by-child correlation matrix [23,48]. Initially, the algorithm places each child (i.e., node) into its own community. In subsequent steps, communities are reassigned until a division of the network into communities is made for which the modularity is optimized. The modularity index Q is a metric that quantifies the quality of the placing of nodes into communities, with higher values indicating better partitioning of the data into communities. In practice, most values of Q fall between 0.3 and 0.7, with values close to 0.3 reflecting weakly defined communities, and values around 0.7 reflecting strong community structures [49]. We used an adapted version of the modularity to take the sign of the weight into account, as we assumed that both positive and negative weights are informative of the similarities and differences between children. Positive weights indicate that two children have similar scoring patterns, and thus provide support that these children should be in similar communities. The more similar the scoring pattern, the higher the correlation,

1 We repeated the community detection analysis based on the item scores of the BFQ-C at T0 with single informant data instead of double informant data for the 15 participants who had both -mother and -father data available. Community outputs and individual classifications remained unchanged.

and the stronger the support for two children to belong to the same community (reflected in Q^+). Negative weights, on the other hand, indicate that two children have opposite scoring patterns. An opposite scoring pattern might indicate important qualitative differences and should thus provide support for children to belong to different communities (reflected in Q^-). Because the community detection algorithm is not deterministic, the optimal number of communities and associated modularity (Q) can differ slightly with different runs. To obtain stable results the final assignment of children was based on the modal group assignment across ten runs.

INTERPRETATION AND REPRESENTATION We compared the identified communities on the personality factors using analysis of variance (ANOVA) tests. Post-hoc tests with Scheffé corrections were performed to determine significant group differences. We visualized the different communities by their patterns on the five personality factors as assessed with the BFQ-C. Moreover, to interpret the communities at a more detailed level, we conducted an exploratory factor analysis on the BFQ-C items. This allowed us to characterize the identified communities at a more detailed personality facet level, similar to Karalunas et al. (2014; 2018) who used the 16 more detailed temperament subscales instead of the three higher order factors. Details on the exploratory factor analysis are given in the Supplementary Material.

STABILITY ACROSS THEORETICAL MODELS Since Karalunas et al. did not include the traits of agreeableness and openness in their model, we also examined the communities obtained by only including the items of the other three personality factors that map onto the factors included in the temperament model (i.e., extraversion, conscientiousness, and neuroticism).

STABILITY ACROSS MEASUREMENT LEVELS Finally, we explored whether the identified communities depend on the measurement level on which the child-by-child correlation matrix was built. We originally estimated the correlation among children based on their scoring pattern on the 65 individual items of the BFQ-C. Alternatively, one could estimate the correlation among children based on their scoring pattern on the five personality factors. We applied the weight conserving modularity algorithm to both matrices and evaluated the stability of the identified communities by computing the correlation between corresponding communities and computing their mean absolute difference.

CLINICAL PREDICTION We evaluated whether the identified communities differed in clinical outcome at T1 as assessed using the SDQ Impact score and the ADHD-RS total score. We first assessed whether the clinical outcomes differed over time using dependent t-tests. Second, we evaluated whether each clinical outcome at T1 could be predicted by community membership, when controlling for baseline SDQ Impact score, baseline ADHD-RS total score, age, and sex. Third, whereas all children were medication free at baseline, some

started treatment after entering into the study. We therefore also evaluated whether the clinical outcomes at T1 were predicted by treatment (yes vs. no), while controlling for baseline SDQ Impact score, baseline ADHD-RS total score, age, and sex. Finally, we explored whether a possible effect of medication on ADHD-RS total score would differ across the communities.

The analyses were conducted in SPSS (version 20) and R (version 3.5.2) using the package 'psych' (version 1.8.12).

7.3 RESULTS

PERSONALITY PROFILES Community detection identified three communities at baseline of 38 (21%), 73 (41%) and 67 (38%) children respectively. The average Q of 0.41 (range: 0.41-0.42) across the 10 runs indicates moderate separation of the three communities. The identified profiles are visualized in figure 7.1A, and the descriptive information is given in table 7.2. For reference, we plotted the profiles next to the average personality factor scores in a normative French sample, that was kindly provided to us by Oliver & Herve (43). The scores in the normative French sample are also included in supplementary table E.3.

Table 7.2: DSM-5 criteria of MDD (left two columns), corresponding IDS items (middle two columns), and included nonclinical complaint abbreviation (right).

Characteristics	Time	Type 1	Type 2	Type 3	Test statistic	Post-hoc
Basic demographics						
N	To	38	73	67		
	T1	38	66	62		
Boys:Girls	To	26:12	55:18	54:13	$\chi^2(2) = 1.98$	
	T1	22:16	53:13	51:11	$\chi^2(2) = 8.81^*$	
Age mean (±SD) years	To	8.5 (1.5)	8.1 (1.3)	8.2 (1.3)	$F(2,175) = 1.40$	
	T1	8.8 (1.4)	8.1 (1.4)	7.9 (1.2)	$F(2,175) = 6.5^{**}$	1>2,3
N(%) on stimulant medication	To	0 (0)	0 (0)	0 (0)		
	T1	20 (52.6)	32 (48.4)	40 (64.5)	$\chi^2(2) = 3.48$	
Comorbidity						
GAD	% at To	15.8	17.8	16.4	$\chi^2(2) = 0.09$	
Specific phobia	% at To	0.0	9.6	1.5	$\chi^2(2) = 7.61^*$	2>1,3
SAD	% at To	5.3	1.4	3.0	$\chi^2(2) = 1.40$	
Social phobia	% at To	0.0	2.7	0.0	$\chi^2(2) = 2.91$	
Enuresia	% at To	2.6	1.4	4.7	$\chi^2(2) = 1.24$	
Encopresia	% at To	0.0	2.7	0.0	$\chi^2(2) = 2.91$	
Tic disorder	% at To	5.3	5.5	4.5	$\chi^2(2) = 0.08$	
ODD	% at To	5.3	9.6	1.5	$\chi^2(2) = 4.33$	
DMDD	% at To	13.1	20.5	6.0	$\chi^2(2) = 6.37^*$	2>3
ADHD and severity measures mean (±SD)						
ADHD-RS total score	To	43.47 (6.28)	41.72 (6.46)	39.35 (6.98)	$F(2,175)=5.09^*$	1>3
	T1	40.76 (8.21)	40.34 (6.16)	42.50 (6.26)	$F(2,175)=1.79$	
ADHD-RS inattentive score	To	22.53 (3.70)	20.26 (4.03)	19.90 (4.15)	$F(2,175)=5.68^*$	1>2,3
	T1	21.37 (4.11)	19.71 (4.42)	20.91 (3.75)	$F(2,175)=2.33$	
ADHD-RS Hyp/Imp	To	20.95 (4.26)	21.46 (3.61)	19.46 (4.61)	$F(2,175)=4.25^*$	2>3
	T1	19.39 (5.45)	20.62 (3.33)	21.59 (3.67)	$F(2,175)=3.54^*$	3>1
SDQ Impact score	To	6.07 (2.64)	6.65 (2.47)	5.28 (2.53)	$F(2,175)=5.15^*$	2>3
	T1	5.86 (2.50)	4.12 (2.77)	5.69 (2.65)	$F(2,175)=7.53^*$	1>2

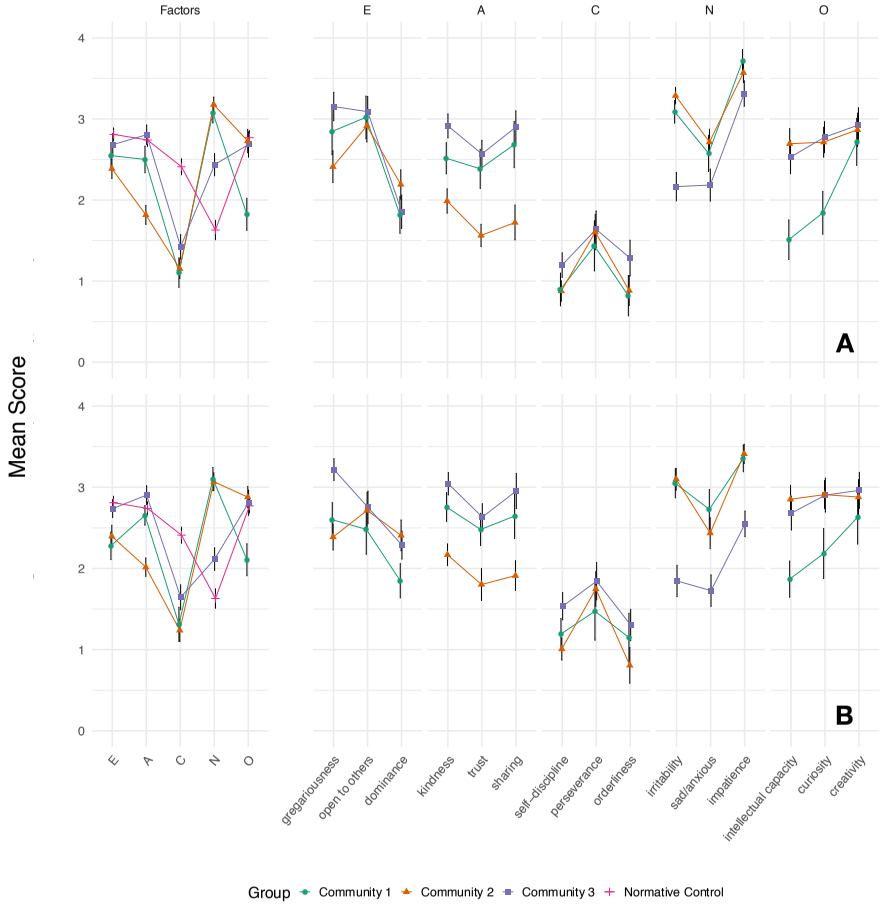

Figure 7.1: Profiles identified at baseline (top) and follow-up (bottom) using the 65 items. Error bars show 95% confidence intervals. Abbreviations: E = Extraversion, A = Agreeableness, C = Conscientiousness, N = Neuroticism, O = Openness to experience.

In terms of personality features, the first profile was characterized by lower openness to experience, specifically in terms of intellectual capacity and curiosity, compared with the other two profiles; and lower levels of conscientiousness when compared with the third profile. The second profile was characterized by a lower level of agreeableness and gregariousness, and a higher level of dominance compared to the other two profiles. Profile 3 displayed high levels of gregariousness, as well as higher levels of agreeableness and conscientiousness compared to the two other profiles. The third profile also showed significantly lower levels of neuroticism, particularly on the sad/anxious and irritability subscales.

Clinically, profile 1 children were significantly more inattentive than the other two types, and displayed higher scores at the global ADHD-RS than profile 3 children. Profile 2 children displayed significantly higher hyperactive/impulsive score than profile 3 children. Finally, profile 3 children presented the lowest ADHD-RS total score.

TEMPORAL STABILITY At follow-up, again three communities were identified, with Q=0.44 (range: 0.44 -0.45), see figure 7.1B. The three communities identified at baseline resembled the identified communities at follow-up well: the correlation between the communities was lowest for community 3 (r=0.89) and high for community 1 (r=0.96) and 2 (r=0.98). This was also reflected in the mean absolute difference across the communities, which was highest for community 3 (0.22±0.19 mean±SD) and community 1 (0.21±0.14 mean±SD), and lowest for community 2 (0.15±0.07 mean±SD). This indicates that the communities are relatively stable over time at a group level. Big-Five personality scores and subscale's score for the three groups at T0 and T1 are presented in supplementary table E.2.

At an individual level, the community-membership was more stable than chance (χ^2=67.97, $p < 0.001$). Overall, 63.8% of the children remained in the same community over time. Stability was highest for children in community 2 (71.0% remained) and 3 (65.0% remained), and lowest for children in community 1 (47.1% remained).

STABILITY ACROSS THEORETICAL MODELS When we used only the items belonging to the three personality factors that match the temperament subscales – i.e., extraversion, conscientiousness, and neuroticism – again three communities were identified, with Q=0.43 (range: 0.42-0.44), see supplementary figure E.2 for the profiles. Comparing the personality profiles identified using three factors to the personality profiles identified using the five factors, the correlation was lowest for community 1 (r=0.88), and high for community 2 (r=0.97) and 3 (r=0.99). Similarly, the mean absolute difference was highest in community 1 (0.38±0.24 mean±SD), and lower in community 2 (0.18±0.11 mean±SD) and 3 (0.12±0.07 mean±SD). The three personality factors that overlap with the temperament model thus capture similar communities compared with all five personality factors.

STABILITY ACROSS MEASUREMENT LEVELS Using the five personality factors instead of the items again three communities were identified, with Q=0.47 (range: 0.46-0.48), see supplementary figure E.1 for the profiles. The three communities that were identified using either the 65 items or the 5 factors resembled each other very well: the correlation among the personality profiles ranged from 0.99-1.00, and the mean absolute difference ranged from 0.05-0.07 (SD range: 0.05-0.06). The high correlations and small differences indicate that the information that is captured in the different items is highly similar compared with the information that is captured in the higher-order factors.

CLINICAL PREDICTION Parent-reported clinical impairment, measured by the SDQ Impact score, decreased significantly from baseline (6.0±2.6 mean±SD) to follow-up (5.1±2.8 mean±SD), $t(165)=4.09$, $p<0.001$. Clinical impairment at follow-up was predicted only by baseline clinical impairment ($t=5.7$, $p<0.001$).

ADHD severity, measured by the ADHD-RS total score, decreased significantly from baseline to follow-up, $t(165)=8.05$, $p<0.001$. Interestingly, ADHD severity at follow-up was predicted by community membership at baseline over and above baseline ADHD-RS total score, baseline SDQ Impact score, age, and sex. Specifically, the decrease in ADHD-RS total score for children in community 1 (-9.3±8.6 mean±SD) was significantly larger than the decrease for both children in community 2 (-4.7±7.5 mean±SD, $t=2.06$, $p=0.04$) and for children in community 3 (-3.5±8.5 mean±SD, $t=2.37$, $p=0.02$). The decrease in ADHD-RS total score did not differ for children in community 2 compared to children in community 3 ($t=0.47$, $p=0.64$).

Between baseline and follow-up, almost half of the children (44.6%) had started medication treatment. We explored whether the start of medication might have affected the clinical outcomes at follow-up. While medication did not predict SDQ Impact score at follow-up, it did predict ADHD severity ($t=-2.40$, $p=0.02$), such that the decrease in ADHD-RS total score was, on average, higher for children who received medication (-7.1±8.9 mean±SD) compared with children who did not receive medication (-3.6±7.6 mean±SD).

Because both community membership and medication predicted ADHD severity at follow-up, we next explored whether the children that received medication were equally distributed across the different identified communities. Note that at baseline, the assessment used to identify the communities, none of the children received medication. Hence, there is no a priori reason to expect that medication and the communities are associated. The percentage of children that received medication was 61.8%, 39.1%, and 41.3% for communities 1-3 respectively ($\chi^2=5.2$, $p=0.08$). Although the difference is non-significant, the relatively high percentage of children that received medication in the first community might explain the larger decrease in ADHD-RS total score in community 1 compared to both other communities.

Therefore, we evaluated whether ADHD severity at follow-up was predicted by community-membership, medication use, or their interaction, while controlling for baseline ADHD-RS total score, baseline SDQ Impact score, age,

and sex. There was a main effect for medication (t=-2.6, p=0.009), but not for community membership ($t<1.1$, $p>0.26$). There was, however, an interaction effect indicating that the effect of medication on ADHD severity in community 1 and community 2 was different compared with community 3 (t=2.77, p=0.006 and t=2.55, p=0.01, respectively). Specifically, medication use was associated to a larger decrease in ADHD-RS total score for children in community 1 (-12.5±8.4 for N=21 medically treated children versus -4.1±6.0 for N=21 non-medically treated children) and 2 (-7.6±7.7 for N=27 medically treated children versus -2.8±6.8 for N=42 non-medically treated children) while this was not the case for children in community 3 (-2.4±7.9 for N=26 medically treated children versus -4.4±8.8 for N=37 non-medically treated children). The effect of medication on ADHD-RS total score did not differ for children in community 1 or 2. This result suggests that the effectiveness of medication treatment might differ for different personality profiles in children with ADHD.

Because the different communities had different ADHD severity at baseline (i.e., 43.47±6.28, 41.72±6.46, and 39.35±6.98 mean±SD for communities 1-3 respectively), we considered the possibility that these baseline differences might confound our finding that medication did not affect children in this third community. To address this issue, we computed the mean ADHD-RS score at baseline for the children who completed both measurements (N=166; 41.24±6.76 mean±SD) and selected only the children in the third community whose ADHD-RS total score was below one standard deviation of that mean (i.e., a score below 34.48). This resulted in selecting 52 of the 67 (77.6%) children, who had a mean ADHD-RS total score at baseline that was similar to that in community 1 and 2 (42.14±5.01 mean±SD). Using only this restricted sample, we re-evaluated our predictive model and still found a significant medication × community interaction effect, indicating that the effect of medication on children in community 3 was different from the children in community 1 and 2 (both $t>1.97$, both $p<0.05$).

7.4 DISCUSSION

In the present study, we set out to replicate the ADHD profiles detected in previous research by Karalunas et al. (2014, 2018) in a new sample of children with combined-typed ADHD, using a different measure of dispositional traits. In line with Karalunas et al. (2014, 2018), the optimal clustering solution yielded three different profiles, and the modularity index robustly stayed in the 0.4 range, reflecting a moderately-defined community structure [49]. The personality profiles themselves were highly stable over time, despite changes in individual classification results.

While we also identified three profiles, we did not identify a profile characterized by emotional lability – labelled as the "irritable profile" by Karalunas et al. (2014, 2018). The differences between the identified profiles might have resulted from the differences in the measurement instrument (BFQ-C versus

TMCQ) and underlying theoretical model (Five Factor Model versus temperament model). However, the BFQ-C and the TMCQ are supposed to share three common higher structure dimensions (De Pauw et al., 2017), and community detection on this restricted set of dimensions did not increase similarity in outputs. Importantly, a recent study investigated the seventeen subscales of the TMCQ, that were used by Karalunas et al. to identify the profiles, in 9-old children and found only little support for the initial theory driven factorial model [32]. As Karalunas et al. (2014, 2018) conducted their analyses based on these subscale scores, this raises the question of whether different profiles might have been identified based on the individual TMCQ items.

Important differences in sample characteristics may also have contributed to divergent findings. First, Karalunas et al. (2018) ADHD sample initially included 26% of children with a purely inattentive ADHD presentation, whereas our sample was exclusively composed of combined-type ADHD cases. Consequently, Karalunas et al. identified profiles may in part, reflect the different types of ADHD cases. This idea is supported by significant differences in the proportions of inattentive and combined types in the different groups identified in their sample (inattentive:combined (% inattentive); mild: 54:30 (64%), surgent: 15:119 (11%), irritable 27:110 (20%)). Current inattentive ADHD cases may include in particular children with sluggish cognitive tempo, a possibly new and different clinical entity, which complexifies the interpretation of findings in mixed ADHD subtypes groups [50,51]. Second, samples were recruited in different geographical areas (USA vs. France), and differences in dispositional traits have been reported in previous research investigating cross-cultural differences in children, with a tendency for lower levels of emotional stability in American vs. European children [52,53]. In this context, whether stable temperamental or personality profiles should be expected in ADHD across different cultures remains an open question. Comorbidity rates, on the other hand, appeared to be comparable (present sample: Anxiety Disorders 19.6%, ODD 5.6%, CD 0%, DMDD 13.5%; Karalunas et al. (2018): Anxiety Disorders 20.6%, ODD 19.3%, CD 1.9%, DMDD 4%), with our sample being possibly more disturbed in the emotional domain (DMDD 13.5% vs. 4%) but less oppositional/defiant (ODD 5.6% vs. 19.3%).

Our profiles also differed from the three profiles that were previously identified using personality questionnaires in a large sample of children and adolescents (6-18 years old): “poor control”, “extraverted”, “introverted [22]. While again the profiles could be mapped in some way (e.g., our first profile resembled the “poor control” group in their high levels of neuroticism and lower levels of openness and conscientiousness) there were also remarkable differences (e.g., whereas our first profile displayed intermediate levels of extraversion and agreeableness, the “poor control” group displayed the lowest levels on these factors). These discrepancies might reflect different sample characteristics such as ADHD presentations (mixed ADHD presentations vs. ADHD combined presentation), differences in age range (a more restricted age range of 6-11 in our sample compared to a larger age range between 6 and 18 years in the study

of Martel [22]), or recruitment strategy (community sample vs. clinically-based). The possible effect of these factors on the identified communities should be examined in future studies.

When examining the predictive value of BFQ-C based profiles, we found that the identified personality profiles were a significant predictor of response to medication. This is a particularly relevant finding since, to date, predictors of treatment effect in ADHD have been elusive. More specifically, controlling for initial ADHD symptom severity, we found that children belonging to the third personality profile did not benefit from the use of medication treatment when compared to the other two groups. Children belonging to this group displayed high levels of gregariousness, as well as high level of agreeableness and conscientiousness compared to the two other groups. They were also characterized by lower levels of neuroticism, particularly on the sad/anxious and irritability subscales. Importantly, this finding did not appear to be confounded by group-differences in initial ADHD severity. Personality measures are easily administered in the clinical setting, and our finding indicate that personality might be relevant to predict treatment response. Researchers trying to predict treatment responders vs. non-responders in ADHD based on machine learning could therefore benefit from including a personality questionnaire among their measures [54]. Whether personality measures will also predict different responses to different types of treatments could further be investigated. Personality measures could ultimately become one of the tools used to provide personalized medicine to children with ADHD.

The profiles themselves were shown to be highly stable over time, whereas the profile-membership of the children was much more variable. Notably, this result was similar to that reported by Karalunas et al. (2018) where the profiles themselves were reproduced over three annual measurements but the membership stability varied between 36 and 66 percent.

Although at first the moderate profile-membership stabilities might cast some doubt on the utility of these profiles for clinical practice, the high stabilities of the profiles themselves are clinically promising. Specifically, even though children might not be assigned to the same group over time, the finding that the profiles are stable over time suggests that there are some stable constellations of personality profiles among children with ADHD. This in itself can have clinical utility, as certain constellations of personality profiles might be predictive of clinical outcomes. It is then this 'state' that is predictive of clinical outcome rather than the stability of the state. This idea is supported by Karalunas et al. (2018) in which they found that belonging to the irritable profile at any point rather than belonging to the irritable profile at all points was predictive for clinical outcomes. The stability of the profiles is especially noteworthy as the children grew older and some started the use of medication. While this might have affected the profile-membership of the children, the profiles themselves were stable regardless of these changes. This again suggests that certain constellations of personality profiles are robust across time.

One potential limitation of our study as well as the previous ones (Karalunas et al. 2014, 2018) is the use of a single parent informant for most cases (91.6%), who could either be the father or the mother of the child. High mother–father agreement for higher order child personality traits has been reported in previous research, with Pearson correlations indexing mother–father agreement ranging from 0.54 for agreeableness and neuroticism to .77 for conscientiousness [55]. Nevertheless, this agreement was not complete, and presence of informant discrepancies might create confusion in research and clinical settings when utilizing ratings to predict later behaviour or to guide assessment and treatment. Presence of informant discrepancies could reflect in some cases underlying conflict in the family system, or the fact that mothers and fathers differentially monitor and evoke some relevant attributes of their child [55]. In separated couples, relevance of each parent's evaluation could also depend on the time they spend with the child based on the custody schedule. In community detection analyses, informant discrepancies could result in different subgroup classifications for borderline individual cases, depending on whether –father or –mother reports are used. Future studies should therefore collect both –father and –mother ratings, in order to compute classification agreement rates, or at least collect data for all cases from the same informant. Another limitation is that there was no control sample, so that we could not compare our identified communities in the ADHD sample to those in a control sample. Yet, this did not affect our main objective to compare ADHD profiles identified using personality measures to those that were identified using temperament measures.

CONCLUSIONS In this study, we examined whether an irritable ADHD profile could be identified in a new sample based on personality dimensions. Three personality profiles were detected, but high ED was not restricted to one of the three profiles, hence an irritable profile was not replicated. The three personality profiles identified, however, yielded unique predictive value, as they were significantly associated with medication effect on ADHD symptoms. Personality questionnaires might ultimately serve to provide more personalized medicine to children with ADHD. Other replication studies using both temperament and personality questionnaires will be needed to clarify whether these divergent findings are due to differences in sample characteristics vs. measurement instruments. Finally, although we did not replicate the ADHD profiles across measures of dispositional traits, it might turn out that both the profiles identified using temperament as well as the profiles identified using personality measures capture unique clinical predictive value.

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8 DISCUSSION

8.1 THIS THESIS

Who are the people suffering from insomnia? What do they have in common, and how do they differ? Why do some continue to develop a depression, while others do not? These questions formed the basis for a series of studies in which we aimed to unravel the heterogeneity in insomnia disorder, and to disentangle the relationship between insomnia and depression.

Noteworthy is that most research questions that we investigated in this thesis have been around for decades. Over forty years ago, in 1976, insomnia was divided into different subtypes based on the dominant sleep complaints [1]; already in 1989 sleep disturbances were found to predict depression [2]; and more recently, in 2015, it was shown that successful treatment of insomnia symptoms also alleviated depression symptomatology [3].

Despite these continuing efforts, the posed research questions have proven to be highly complex. The insomnia subtypes based on the dominant sleep complaints, for example, turned out to be very unstable [4] and were discarded from nosologies as they did not benefit diagnostic accuracy [5]. Moreover, considerable overlap in the symptoms of insomnia and depression raises questions on their empirically identified relationships: could the increased risk and the observed treatment effect largely reflect this symptom overlap?

In this thesis we have tried to unravel insomnia heterogeneity and disentangle the relationship between insomnia and depression, while taking these considerations into account. To do so, we expanded our focus beyond the diagnostic criteria of insomnia and depression, and used new statistical methodologies. As a result, most projects in this thesis unify conceptual and clinical research questions with methodological innovations.

INSOMNIA: SUBTYPES IN SYSTEM RATHER THAN SYMPTOM In the first part of this thesis we reconsidered the question of insomnia heterogeneity. Instead of an exclusive focus on sleep and its related characteristics, we expanded our perspective: What if there are subtypes of insomnia disorder that are not directly reflected in the sleep characteristics themselves, but relate to other characteristics such as personality, affect and life history, that form the context in which insomnia is developed and maintained?

Such a wider perspective enabled us to identify five subtypes of insomnia disorder: highly distressed, moderately distressed but reward sensitive (i.e., with intact responses to pleasurable emotions), moderately distressed and reward insensitive, slightly distressed with high reactivity (to their environment

and life events), and slightly distressed with low reactivity. The subtypes were stable over time and across samples.

Crucially, the identified subtypes were not primarily distinguished by clinical demarcations of the insomnia complaints 'difficulty initiating sleep' (DIS), 'difficulty maintaining sleep' (DMS), or 'early morning awakenings' (EMA); nor by comorbid sleep disorders. Rather, each subtype was determined by a multivariate pattern of stable characteristics of personality, affect, and life history. The subtypes thus reflect *distributed differences* as no single characteristic can differentiate among the subtypes; it is the multivariate *fingerprint* of specific combinations that is unique to each subtype. The finding that many different characteristics were important to identify subtypes of insomnia underlines the potential to approach insomnia as a complex system; where many different factors form the context in which insomnia can occur and be maintained.

INSOMNIA AND DEPRESSION: DIFFERENTIAL ROLE OF SYMPTOMS In the second part of this thesis we aspired to disentangle the close link between insomnia and depression by deconstructing both disorders into their network of interrelated symptoms. This network conceptualization enabled us to prospectively and concurrently evaluate whether specific symptoms have differential roles in the development and treatment of depression.

By incorporating first-onset depression occurrence over six-years follow-up into this network, we could reveal that specifically the insomnia complaint *difficulty initiating sleep* directly and prospectively predicts first-onset depression. Similarly, incorporating treatment as a node (variable) into the network of correlated symptoms allowed us to identify sequential and specific treatment effects over time. This Network Intervention Analysis elucidated direct and indirect treatment effects and revealed that cognitive behavioural therapy for insomnia (CBTI) primarily affected the insomnia complaints *difficulty maintaining sleep* and *early morning awakenings*. This suggests that the likely route for CBTI to affect depression symptoms is through its effect on these sleep complaints.

STRUCTURE IN COMPLEX SYSTEMS: PSYCHOPATHOLOGY AND ADHD In the final part of this thesis we departed from our main focus on insomnia and depression and investigated psychopathology in general (chapter 6) and ADHD in particular (chapter 7). In both projects we aspired to find subgroups: how do different symptoms of psychopathology cluster together? Can we identify subtypes of children with ADHD?

In order to investigate the possibility of subgroups, we represented both the psychopathology symptoms and the children with ADHD as networks: In the psychopathology network the nodes represent symptoms connected by edges that represent their co-occurrences; whereas in the ADHD network the nodes represent children and the edges indicates the similarity in their personality profile. Based on this representation we subsequently used data-driven community detection to evaluate whether there is structure within this network.

In the psychopathology network, we identified groups of symptoms that cluster together into 'problem areas', and we proposed to focus on the differential role that symptoms can have within and between problem areas – as stabilizing or communicating. Stabilizing symptoms that show many and strong connections within a problem area could be thought of as the core (i.e., hallmark symptoms), whereas communicating symptoms that belong to multiple problem areas facilitate 'communication' (i.e., comorbidity) between problem areas.

Among the children with ADHD we identified three clusters based on their personality profiles. While over time some of the children switched clusters, the profiles themselves were highly stable over time, indicating that there are some stable and robust constellations of personality profiles among children with ADHD.

It is notable how these final two projects are ingrained in the earlier chapters as we aspired to find subgroups (similar to our aim to identify insomnia subtypes in chapter 3) by using a network-representation (as we used to identify the link between insomnia and depression in chapters 4 and 5). Following from these projects combined, there are two conclusions that transcend the individual projects.

First, the identification of subgroups might benefit the most from taking a multivariate approach in which it is the specific combination of characteristics that matter. A high neuroticism score might not capture a single robust insomnia type, but together with a high positive affect score it does. Similarly, a high openness score alone cannot differentiate between children with ADHD, but together with a low agreeableness score it can. For both insomnia and ADHD these multivariate profiles turned out to be highly stable over time, underlining the possibility that such profiles could represent different 'stable attractor states'.

Second, whereas multivariate profiles might be best to identify stable subgroups, a specific focus on individual symptoms might be optimal to gain insights into more fine-grained dynamics. Which symptoms form the 'bridge' between two disorders as 'communicating symptoms'? And are the symptoms that may trigger the onset of a co-morbid disorder also the symptoms that promote recovery? Our symptom-specific results where DIS prospectively predicts depression onset whereas DMS and EMA are important in alleviating depression symptomatology suggests that this does not need to be the case.

8.2 BEYOND THIS THESIS

The findings and explorations in this thesis may stimulate new *clinical*, *theoretical*, and *methodological* avenues.

8.2.1 *clinical avenues*

Clinically, the findings in this thesis may provide clues to personalize the treatment of insomnia and to prevent or treat depression through successful treatment of insomnia symptoms.

PERSONALIZED TREATMENT OF INSOMNIA Our identification of insomnia disorder subtypes opens up important new possibilities to pursue personalised and optimised treatments of insomnia disorder. One important implication of the identified subtypes is that they emerged as multivariate profiles of stable characteristics not directly related to sleep. Consequently, to advance our understanding of mechanisms underlying insomnia and reveal biomarkers such that we can optimise treatments, we must go beyond the original clinical demarcations.

First, it would be extremely valuable to expand the identified subtypes across different levels of information; from self-reported behaviour to biology. We were already able to show that reactivity in the low distressed high reactive type (subtype 4), that we initially identified using self-reported behaviour, was reflected in a neurophysiological biomarker as well. This cross-level consistency supports that the identified high reactive subtype exists beyond self-reported signs and symptoms, meeting an important goal of the Research Domain Criteria [6] and opening up opportunities for subtype-specific pharmacotherapy.

These cross-level studies should ideally be extended to all subtypes. For example, the fingerprint of the moderately distressed reward sensitive subtype (2) clearly identifies 'pre-sleep arousal' and 'insomnia response to stress' as important contributors. Accordingly, this subtype resembles the conventionally labelled psychophysiological insomnia. This resemblance can provide a wealth of information. On the one hand, we can use the models on psychophysiological insomnia to inform us on possible mechanisms that may play a role in subtype 2, such as heightened cortisol levels [7]. At the same time, by targeting people with insomnia subtype 2 specifically, we can reduce previous unrecognized heterogeneity, resulting in more power to elucidate robust subtype-specific mechanisms. This approach might resolve past inconsistencies, like conflicting findings on cortisol abnormalities in psychophysiological insomnia [7].

It is interesting to note here that these past inconsistencies might reflect different subtype-distributions across studies, depending on in- and exclusion criteria. For example, recruiting patients from a clinical population will likely result in including the highly and moderately distressed types 1–3, while studies that exclude patients with current depression complaints will exclude mostly type 1 and 3, that have the highest current mood problems (36.4% and 18.7% respectively). By revealing these subtypes, future studies can evaluate whether inconsistencies across studies might be due to different subtype representations.

Second, at the behavioural level, subtyping enables us to tailor treatments based on the specific *fingerprint* unique to each subtype. This would allow to directly test our hypothesis that these characteristics play a role in the develop-

ment and maintenance of the disorder. For example, as we also discussed in chapter 3, specific treatments that focus on reducing pre-sleep arousal, such as meditation intervention, might be especially beneficial for people with insomnia disorder of subtypes 1, 2, and 3 that are characterised by high pre-sleep arousal, and not for those with subtype 4 and 5. These specific hypotheses allow future studies to investigate whether these personalized subtype-tailored treatments outperform more standardized one-size-fits-all treatments that are mostly used today.

DIFFERENTIAL ROLE OF SLEEP COMPLAINTS IN THE DEVELOPMENT AND TREATMENT OF DEPRESSION Evidently, the findings in chapter 4 and 5 that particular sleep complaints are important in either the development or recovery of depression could have important clinical implications, given the high prevalence [8] and recurrence rates [9] of depression.

We could try to meet the global priority [10] to *prevent* depression by targeting the sleep complaint DIS. We might even be able to prioritize individuals that run the highest risk, by integrating this finding with our identified subtypes. Among the five types, the highly distressed subtype (1) and the moderately distressed reward insensitive type (3) had the highest lifetime and current prevalence of mood complaints, as well as strongly diminished positive affect which has been suggested to be predictive of depression onset [11]. Combined, these findings suggest that people with types 1 or 3 insomnia that suffer from DIS run the highest risk of depression. Future studies can test this hypothesis and evaluate whether successful treatment of DIS mitigates the risk of depression.

When prevention of depression fails, targeting co-occurring insomnia symptoms might still offer an opportunity to treat depression complaints. The finding that CBTI primarily targets DMS and EMA after which also the depression symptoms abate, highlights the possibility to *treat* depression through treatment of insomnia. Taken together, insomnia is a key determinant in both the prevention and treatment of depression, and thereby provides multiple ways to combat the global burden of disease that depression poses today [12].

Crucially, these findings moreover highlight the possibility that there might be multiple separate pathways connecting insomnia and depression. When someone is not depressed (i.e., in a healthy state) developing the sleep problem DIS but not DMS or EMA might 'open up' the way to develop a depression, as illustrated in the top row in figure 8.1. In contrast, when in a depressed state, it might not be DIS but rather DMS and EMA that are important to target in order to 'open up' the pathway back to a healthy state, as illustrated in the bottom row of figure 8.1.

Such an hypothesis stresses the possibility that symptoms can have differential roles and dynamics, and that the way "towards" a disorder does not need to be the best way to get "out of" that disorder. Investigating this hypothesis could advance clinical approaches to prevention and intervention.

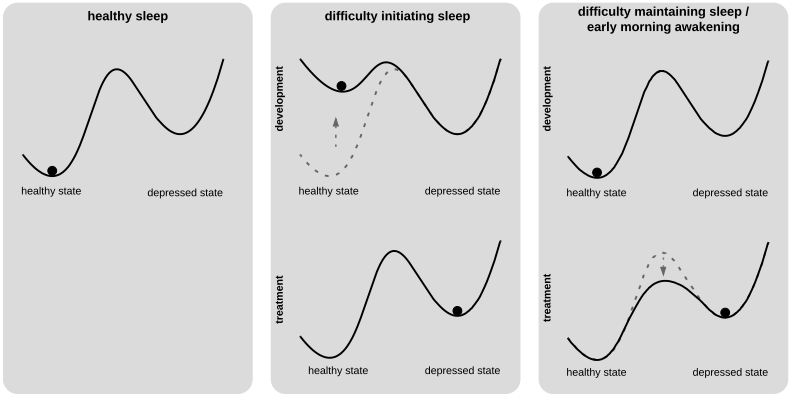


Figure 8.1: Representations of stability landscapes with a healthy and depressed attractor state. The ball represents the current state that the system is in. The shape of the landscape can be influenced by factors, like sleep. When the system is in the healthy state (top row) and without sleep problems (left panel), there is a deep basin of attraction that indicates that the healthy attractor state is stable and that a large 'perturbation' of the system is needed to transition from the healthy to depressed attractor state. When someone in the healthy state (top row) develops a sleep problem (middle and right panels) its effect on the stability landscape might be different, depending on the particular sleep complaint. Possibly, especially the sleep problem DIS alters the stability landscape in such a way that the healthy state becomes less stable, so that only a small perturbation is required to transition from the healthy into the depressed attractor state. Similarly, when the system is in the depressed state (bottom row), it could be that the stability landscape is now only influenced by DMS and EMA, such that treatment of these symptoms alters the landscape and makes it easier to transition back to the healthy attractor state.

8.2.2 *theoretical avenues*

INSOMNIA AS A *complex* SYSTEM In the introduction of this thesis we briefly considered insomnia as a complex system, representing a landscape with two attractor states of healthy and disturbed sleep. At that point, we used the complex system paradigm more as an analogy to broaden our perspective on possible factors that could be relevant to the heterogeneity that is observed in insomnia. Throughout the projects included in this thesis we have more directly touched upon this complexity approach by investigating insomnia and its relation to depression from a network perspective. Yet, we did not explore the potential of formally proposing insomnia as a complex (dynamical) system.

Complex systems consist of *components* that can *interact* at a more 'local' scale, such that at a more 'global' scale self-organizing structures or behaviours can arise [13]. In psychopathology, this approach has been formalized into the network theory of mental disorders, where interacting *symptoms* at the local level can result in organized behaviour as a mental *disorder* at the global level [14]. Interestingly, the diagnosis of an insomnia disorder explicitly captures such direct relations among its symptoms – as the complaints at night should subjec-

tively *cause* daytime impairments in order to qualify for a clinical diagnosis of insomnia [15].

When the interacting components in a complex system form self-reinforcing, positive feedback loops, this can cause the complex system to have multiple stable attractor states [16]. Again, for the case of insomnia, positive feedback loops seem very plausible across multiple levels. Not only at the behavioural symptom level there is a clear feedback loop ('difficulty initiating sleep' → 'fatigue' → 'concentration problems' → 'worry about sleep' → 'difficulty initiating sleep'); also at the cognitive and biological level are there indications for positive feedback loops.

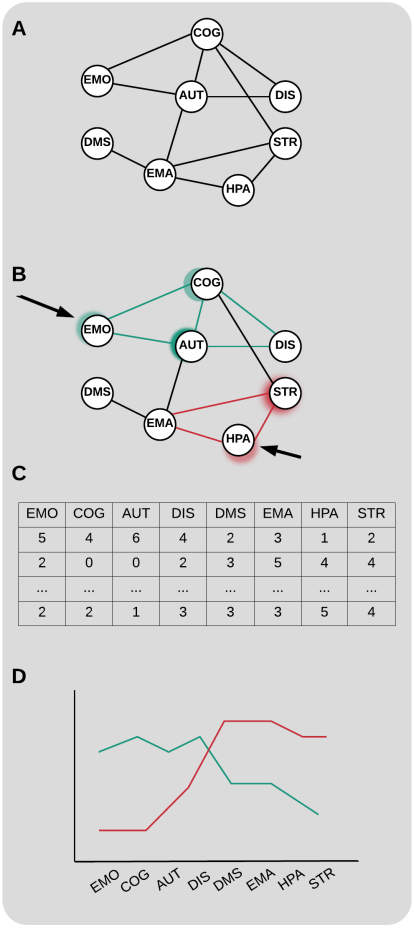
The cognitive model of insomnia, for example, identifies positive feedback loops between cognitive activity, autonomic arousal, and emotional distress, that accumulate into an insomnia disorder [17]. Biologically, according to a physiological model of insomnia, there is vicious cycle of insomnia with the hypothalamus-pituitary-adrenal (HPA) axis – a neuroendocrine system that is involved in stress: heightened activity in the HPA axis can promote insomnia, and insomnia itself can activate the HPA axis [18].

It would be valuable to incorporate the three levels of biology, cognition, and behaviour, and see how these factors relate to one another (figure 8.2 A). By empirically estimating these relationships, we could subsequently evaluate whether different pathways through this system exist (figure 8.2 B-C) that would result in differential symptom patterns that we also currently observe in clinical practice (figure 8.2 D).

Thus, the direct interactions and positive feedback loops across the levels of biology, cognitions, emotions, and behaviour highlight the suitability of modelling insomnia as a complex system. An integrated model of insomnia that incorporates these different levels could provide new ways to unravel mechanisms underlying insomnia. Ultimately, when such a model can explain observed clinical phenomena (e.g., differential symptoms patters), we might go beyond what we currently know and find new ways to learn about insomnia mechanisms, treatment, and prevention.

INSOMNIA AS A COMPLEX *system* Central to the concept of insomnia as a complex system, are the associations among the symptoms. According to the vulnerability hypothesis, the strength of these associations captures the vulnerability (or resilience) of the system [14,19]. Especially in the case of insomnia, it is likely that a bad night sleep is related to 'fatigue' and 'concentration problems' for the majority of the population. Yet, not for everyone does a bad night sleep result in daytime impairments. What then differentiates the people with insomnia from the people without?

Possibly, (among other things) it is the strength of these associations: for someone who is vulnerable to insomnia a night of bad sleep might have much worse daytime consequences than for someone who is resilient [20]. At the same time, different studies including ours in chapter 5, have shown that over



EMO	COG	AUT	DIS	DMS	EMA	HPA	STR
5	4	6	4	2	3	1	2
2	0	0	2	3	5	4	4
...	...	...	...	...	...	...	...
2	2	1	3	3	3	5	4

Figure 8.2: One possibility to try and incorporate biology, cognition and behaviour. Based on the existing literature and different models across all three levels we can identify factors that are thought to be of relevance to insomnia. We could then empirically estimate how these factors relate to each other (A). Following earlier work on depression [17] we could use this empirically estimated model to subsequently investigate specific hypotheses. We could explore, for example whether different pathways through this system might exist. Perhaps one pathway to sleep complaints might exist from dysregulation in the HPA system, whereas another might originate from emotional distress (B). Using simulation studies, we could test whether such potential pathways would result in differential symptom patterns that we also observe in clinical practice (C). Finally, we could evaluate whether such patterns result in distinguishable subtypes (D). This way we might ultimately be able to link our identified subtypes in chapter 3 to insomnia as a complex system. Abbreviations: AUT = autonomic arousal; COG = cognitive activity; DIS = difficulty initiating sleep; DMS = difficulty maintaining sleep; EMA = early morning awakening; EMO = emotional distress; HPA = HPA axis; STR = stress.

the course of treatment, the network structure changed [e.g., 21] and became more connected [e.g., 22].

The relationship between the structure of the network, vulnerability, resilience and treatment, is thus not trivial. It could be that both the disordered *and* the healthy state are represented by a strongly connected network, which could be interpreted as a system that gets *locked* into a state. This would imply, however, that symptoms and their direct interactions are not only indicators of problems ('sleep complaints' → 'daytime impairments'), but also of the absence of problems ('*absence* of sleep complaints' → '*absence* of daytime impairments').

It would be extremely valuable to explore whether such a theoretical system could hold, as it would offer direct implications for the prevention and treatment of insomnia – and mental disorders more generally. If indeed the system

could get 'locked' into either a healthy or disturbed state, we would want to respectively stimulate or rather break strong connectivity, depending on the state someone is in. For someone with sound sleep, we would want to stimulate the connections of '*no* sleep complaints' → '*no* daytime impairments'. In contrast, for someone with insomnia we would first want to weaken the network, and break the connection 'sleep complaints' → 'daytime impairments', before we can stimulate and strengthen the new connection of '*no* sleep complaints' → '*no* daytime impairments'.

This conceptualization would be supported by recent findings that destabilization of the network was associated with better treatment outcomes [23], and with the finding that treatment responders initially had a more weakly connected network than non-responders, and showed the largest increase in connectivity over the course of treatment [22]. Using simulation studies we could evaluate whether such a theoretical model might underlie these observed clinical phenomena, or whether alternative accounts are more plausible. Together, by linking the empirically observed clinical phenomena to a theoretical model, we might be able to further formalize vulnerability, resilience, and treatment of insomnia, which can ultimately guide us towards prevention and treatment.

INSOMNIA AS A COMPLEX *dynamical* SYSTEM Finally, one important avenue that could open up by conceptualizing insomnia as a complex system with different stable states of healthy and disturbed sleep, would be the identification of transitions between these stable states by so called *early warning signals*. Early warning signals are generic properties that, across different complex systems, have been observed to precede abrupt transitions from one stable state to another [24]: the onset of an epileptic seizure [25], changes in climate [26], and the onset of depression [27] were all shown to be preceded by such early warning signals.

By modelling insomnia as a complex system of different interacting entities of biology, cognitions, emotions, and behaviour, we could evaluate - over time - whether a transition between healthy and disturbed sleep is preceded by similar early warning signals. If we would find reliable indicators of these transitions, we might eventually be able to predict these changes; enabling us to identify individuals at risk and offering opportunities to prevent the onset of insomnia.

To model insomnia as a complex system over time also highlights an important line of research that we have so far not considered in this thesis: the modelling of dynamic interactions *over time*. The concept of time seems especially applicable to insomnia, as sleep complaints and their daytime consequences are inherently related over time. By incorporating this aspect of time into the analysis, we might complement our view on vulnerability, resilience, and treatment effects. Can we identify vulnerable individuals by their day-to-day dynamics? How does treatment affect these relations over time? Does treatment impact the symptoms directly, does it affect the relationship among these symptoms, or

does it change something in the 'external field', not directly incorporated into the system?

8.2.3 *methodological avenues*

Throughout this thesis we tried to optimize methodologies to investigate our conceptual research questions. To this end, we also introduced Network Intervention Analysis (NIA) to investigate sequential and symptom-specific treatment effects. While NIA already proved to be a useful technique, developing this analysis further could enhance its potential even more.

EXTENDING NETWORK INTERVENTION ANALYSIS First, it would be valuable to extend NIA into a *directed* NIA. Currently NIA estimates an undirected network, meaning that we cannot infer the directionality of the relations among symptoms. We are, however, asking a *directed* question: which symptoms are affected by treatment and how does this effect spread through the network? We thus want to know whether the change in one symptom, caused by the treatment, directly affects change in other symptoms.

Crucially, since people were randomised to treatment, we know for a fact that any estimated 'undirected' effect between treatment and symptoms is actually directed. Upon randomisation it is, of course, impossible for the symptoms to causally affect the treatment conditions. By extending NIA to incorporate this information when estimating the network, we can with much more certainty determine the directionality of the effects between symptoms and determine likely causal pathways [28]. Using *directed* NIA we can then gain insights into the trajectories of symptom changes and the potential of intervening on particular symptoms.

Second, treatments might affect not only symptoms themselves, but also the interactions among symptoms. During cognitive behavioural therapy for insomnia, for example, it is tried to break the link between 'sleep disturbance' $\rightarrow$ 'worry about sleep'. The mixed graphical models used in NIA have been recently extended to incorporate moderation effects [29]. This would allow to extent the current NIA to also estimate whether treatment targets associations between symptoms.

Third, NIA could become more powerful if it would integrate similarities across assessments. NIA now estimates a network for each assessment separately, thereby ignoring the repeated measurements structure of the data and complicating the comparison of the network structure over time. Using newly developed methods [30], we might be able to exploit similarities across the measurements while at the same time allowing the structures to differ. This way we would increase our power to interpret differences in network structures across measurements in a meaningful way.

PSYCHOPATHOLOGY NETWORKS & THE SPECIAL CASE OF INSOMNIA AND DEPRESSION In interpreting estimated psychological networks, both in this thesis and in the broader literature [31], the focus is often on the direct interactions between nodes. This interpretation is grounded in the network theory of mental disorders, where mental disorders are postulated to arise from direct interactions among symptoms [14]. Yet, for this parallel to hold, it is essential to consider the constituents of our empirically estimated networks: are the nodes valid and reliable measures of symptoms? Do the estimated associations among symptoms indeed reflect direct causal connections?

In practice, nodes often constitute single items from questionnaires. Given that many questionnaires are constructed to measure a single underlying construct, these items might not be most optimal from a network perspective because of their so-called 'topological overlap' [32,33]. Similarly, in estimating a network we must carefully consider the nodes we include, as omitting important variables can lead to estimating a direct relation between two symptoms (e.g., 'depressed mood' and 'fatigue') when both are in fact caused by a third variable (e.g., 'insomnia') [34]. Finally, to empirically evaluate the causal nature of the direct relations among symptoms as posited in the network theory is highly challenging. One strategy that has been proposed is the use of experimental data [34,35]: does the manipulation of one 'node' (symptom) directly affect the other nodes in the network? But how to target a single, specific symptom?

Studying depression and insomnia from a network perspective might offer unique opportunities to some of these challenges. First, at least part of the network of insomnia and depression can be well delineated as some symptoms are nocturnal, whereas others are diurnal. This temporal ordering between (some of) the symptoms captures unique information on the (bi)directional relations between sleep and mood. Second, and fundamental to the network theory, it is possible to target specific nodes. Cognitive behavioural therapy for insomnia involves a strong behavioural component through sleep restriction that exclusively targets the nocturnal sleep complaints. The availability of such targeted interventions for insomnia could provide an unparalleled opportunity to empirically test the outstanding hypothesis of causal interactions among symptoms.

8.3 CONCLUDING REMARKS

While I tried to label different future avenues as either clinical, theoretical, or methodological, it became increasingly clear that these three domains are tightly interwoven. Observed clinical phenomena can guide us towards a theoretical model, and developing a successful theoretical model can itself inform us on possible clinical implications. In between, methodological simulation studies are needed to translate and test the theoretical models; and methodological innovations can be used to shed new light on possible clinical processes. In short, none of these realms can exist without the other.

In my view, integrating the clinical, theoretical, and methodological domains in which we incorporate biology, cognition, emotion, and behaviour will be the way forward to further increase our understanding of insomnia and its relation to depression. An understanding that must ultimately lead to early detection, prevention, and optimal personalised interventions.

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Part IV

APPENDICES

A

SUPPLEMENT TO 3: INSOMNIA SUBTYPES

A.1 SUPPLEMENTARY METHODS

A.1.1 *Latent Class Analysis*

A.1.1.1 *Model estimation*

To identify subtypes of ID, a model-based clustering technique was chosen as it can (i) handle missing data; (ii) include variables that are measured on different scales; and (iii) classify new cases [1]. All participants who completed at least one of the questionnaires (N=2224) were included in the latent class model estimates. Irrespective of missing data, the Latent GOLD software package can optimally use all available information to estimate the model [1]. The characteristics were entered as continuous variables, except for *Insomnia in family*, which was binary (0: 'no family member suffers from insomnia', 1: 'at least one family member suffers from insomnia'). Models were estimated starting with an Expectation-Maximization algorithm and switching to Newton-Raphson when close to the final solution [2]. All Default settings of Latent GOLD were used except for an increase in the number of random initial parameter sets from 16 to 100, in order to better avoid local minima. A model with 5 latent classes had the lowest Bayesian Information Criterion (BIC) score, computed according to the formulas below. To evaluate whether findings depended on scale type specification, we ran ancillary models that specified the scaling of variables as ordinal rather than continuous. The results did not differ substantially, which supports the robustness of the main results. For clarity of presentation, in the main text we only report the models with continuous variables. Results for the ordinal scale type specification can be provided upon request.

$$L^2 = 2 \sum_{i^*=1}^{I^*} n_i \times log \frac{n_{i^*}}{\hat{m}_{i^*}}$$

$$BIC_{L^2} = L^2 - log(N)df$$

Where, i^* indicates the unique patterns in the dataset, with observed frequency count n_{i^*}; $\hat{m}_{i^*}$ denotes the estimated cell count for data pattern i^*; and N is the total sample size. For a complete explanation on how to compute the BIC statistic, we refer to the technical guide of LatentGOLD (p. 67-69) [1].

A.1.1.2 *Model evaluation*

We classified participants using the five-class model and evaluated the misclassification error by the *median posterior class-membership probabilities* and the *classification error*. The median posterior class-membership probabilities indicate the certainty with which participants are assigned to a specific class. More specifically, each participant has a posterior probability to belong to each of the classes, which together sum to one. Participants are then assigned to the class for which this posterior probability is highest, and the median posterior probabilities among all participants assigned to a certain class can be computed. The classification error is an estimation of the proportion of participants that are misclassified across all classes.

The certainty with which a participant is assigned to a specific class logically depends on the number of available scores. Therefore, we evaluated these measures first across all participants, and subsequently for subsamples with more stringent inclusion criteria, by stepwise increasing the required minimum number of completed variables for a participant to be included. Including all participants, the estimated classification error was 28% and the median posterior classification probabilities varied between 0.64 and 0.86. Requiring a minimum of 10 available characteristics resulted in a dataset of N=1,046 in whom classification error was acceptable (13%) and posterior classification probabilities were high across all five classes (range: 0.91-0.99).

A.1.1.3 *Assumptions*

The local-independence assumption of a latent class model states that the scores on each pair of characteristics are unrelated (i.e., statistically independent) within a class. To evaluate this assumption, the residual relation among scores of two characteristics within a class is estimated. When the residual relation between two characteristics (called the bivariate residual [BVR]) is substantially larger than 1, this indicates model misfit [3]. Latent class models allow one to address violations of the local independence assumption by including additional 'direct effect' parameters that captures the remaining association between characteristics. The gain in model fit relative to the cost of estimating extra parameters can be evaluated by, e.g., the BIC.

We stepwise added a parameter for each next largest bivariate residual until the BIC was minimised. The BIC minimum was found after adding only one parameter to account for the bivariate residual between *duration* and *severity of insomnia response to life events* (BVR=16.7). This resulted in a somewhat better model, as indicated by a lower BIC of 134858.6 as compared to 134908.9. Adding more parameters would again increase the BIC. Because the interpretation of the subtypes did not change substantially by inclusion of a single parameter, we describe the simpler model without the added parameter for reasons of clarity.

The latent class model moreover assumes that the data are missing at random (MAR). This means that that probability for a score to be missing can be related to the observed data, but not to the missing data itself. For example,

to meet the MAR assumption, the propensity of a missing value on, e.g., the perfectionism scale must be unrelated to someone's perfectionism score. Since the missing values are unobserved, this assumption cannot be validated in practice. However, the Sleep Registry implements data-assessment in a way that maximizes the chance that data are missing at random, by e.g., listing the questionnaires in a random order that differs for each participant and each occasion.

A.1.2 *Developing the Insomnia Type Questionnaire (ITQ)*

There were two main criteria when developing the Insomnia Type Questionnaire (ITQ). First, the ITQ has to be available for independent use and therefore must include the Insomnia Severity Index to identify probable ID cases. Second, the ITQ must, as much as possible, restrict the number of items and eliminate items that users consider difficult to answer. These steps will encourage widespread implementation. We therefore first select the most discriminating characteristics, and subsequently tuned the ITQ by replacing or excluding some of the items.

A.1.2.1 *Selection of most discriminating characteristics*

To select the most discriminating characteristics we used the estimated posterior class-membership probabilities of the N=1046 participants with ID and $\geq$ 10 completed characteristics as outcome in a generalized linear model. As predictors, we included the available observed scores on the 26 characteristics. Crucially, we used $\lambda 1$ (lasso) regularization to select a minimal subset of characteristics that can still adequately predict the posterior class-membership probabilities. The lasso shrinks regression coefficients and puts others to be exactly zero, whereby it selects a subset of predictors. Notably, in selecting the optimal subset of predictors, lasso regularization will select just one of highly correlated predictors.

In addition, to control for false discoveries we used stability selection [4]. Stability selection applies the feature selection algorithm, in our case a generalized linear model using lasso regularization, to subsets of the data with different subsets of features. The results are aggregated over subsets and indicate how often a feature was selected, while controlling the per-family wise error rate. Two out of three parameters have to be specified: the maximum per-family wise error rate $PFERmax$, the threshold for selection probability π_{thr}, and the number of selected variables per subset q. We specified the $PFERmax$ and the π_{thr} parameters following the guidelines proposed by Hofner et al. [5]. Given that we do not want to miss any characteristic that might be important to differentiate among classes, we selected a $PFERmax$ of 1.3 and π_{thr} of 0.75.

Whereas missing data are not a problem in estimating latent class models, missing data cannot be handled by the generalized linear model used to select the optimal subset of discriminating characteristics. Missing values were therefore imputed. Participants were selected to have completed at least 10

characteristics. The median was 19 out of 26 completed characteristics (73%). In total 6873 out of 26150 entries (26%) had to be imputed. To minimize the effect of a single specific imputation method on selected characteristics we used different methods: multiple imputation ($m = 5$), imputing data from the overall observed distribution, and from the class-specific distribution. We selected the characteristics that were selected in at least one of the models.

Depending on imputation method, between 13 and 17 characteristics were selected. Together, 19 characteristics were selected at least once: *insomnia age of onset*, *lack of action control* (Action Control Scale), *lack of agreeableness*, *lack of extraversion*, *neuroticism* (subscales of Mini-IPIP), *lack of behavioural activation* (subscale of the Behavioural Inhibition / Activation Scale), *fatigue* (Fatigue Severity Scale), *insomnia response to stress* (Ford Insomnia Response to Stress Test), *severity of insomnia response to life events* and *duration of insomnia response to life events* (Life Experiences Survey), *negative affect* and *positive affect* (Positive and Negative Affect Schedule), *perfectionism* (Perfectionism Inventory), *lack of positive rumination* and *dampening of positive moods* (Response to Positive Affect), *pre-sleep arousal* (Pre-Sleep Arousal Scale), *rumination* (Reflection Rumination Scale), *lack of subjective happiness* (Subjective Happiness Scale), *lack of experiencing pleasure* (Temporal Experience of Pleasure Scale). These 19 characteristics formed the basis for the Insomnia Type Questionnaire (ITQ).

A.1.2.2 *Reducing the number of questions*

Including all characteristics that were selected at least once (listed above) to form the ITQ, supplemented with the Insomnia Severity Index (ISI), would result in 323 questions. The large number of items would require much time to complete the ITQ. Therefore, we investigated ways to reduce the number of questions of the longest selected questionnaires: Life Experiences Survey (LES; 120 items) and the Perfectionism Inventory (PI; 60 items).

We tried to develop a shortened version of the LES, by selecting 16 life events that, based on all completed records in the Sleep Registry (N=3935), most individuals experienced and indicated to have affected their sleep. We combined these 16 events into five questions covering different domains: relationships, health, housing, job, and financial status. Test-retest correlations however showed that this reduction was unsuccessful. We choose to replace the adjusted LES for the Childhood Trauma Questionnaire (CTQ), as the CTQ differed strongly between subtypes (subtypes explained 26% of the variance in CTQ), and differentiated particularly well the same subtypes that the LES differentiated. Moreover, the CTQ has good test-retest reliability [6,7].

To minimize the number of questions for the PI, we predicted the PI total score by its subscale scores for all completed records in the Sleep Registry (N=2500). Using best subset selection (implemented in the R-package 'leaps' [8]), we evaluated the proportion of explained variance in PI total score using different subsets of subscales. Three subscales (*organization*, *parental pressure*, and *rumination*) explained 90% of the variance, and adding a fourth (*concern*

over mistakes) resulted in only a minimal increase in the proportion of explained variance increased to 93%. We therefore used three subscales to estimate a linear model to predict perfectionism total score. Test-retest correlations of $r = 0.77$ showed that this subset of questions was a good approximation of PI total score.

Finally, one characteristic (*insomnia age of onset*) was reported to be difficult to estimate by many participants. Therefore, we excluded these questions from the final ITQ.

The resulting ITQ contained 200 questions.

A.1.2.3 *Descriptive information of sample recruited for follow-up*

Of the N=1046 participants who were originally classified, we contacted a random subsample N=450 participants to fill out the Insomnia Type Questionnaire (ITQ). Between April 13th and May 1st 2017 N=215 participants completed the ITQ (response rate 0.51%). The subsample was representative of the N=1046 in terms of subtype distribution, age, and sex.

At follow-up, the mean Insomnia Severity Index (ISI) score (mean±SD 13.6±4.6) was lower than at the first assessment (mean±SD 15.9±5.5; $t(214) = 6.54, p < 0.001$). On average, the ISI score decreased by 2.3 points (SD 5.2, range: -21 to +10) between measurements. Nevertheless, only N=43 (20%) participants had an ISI score below the original selection criterion of 10, supporting the chronic nature of Insomnia Disorder. Inspecting the individual insomnia complaints revealed that the severity of all complaints decreased from the first assessment to follow-up (all $t(214) > 2.72$, all $p < 0.007$): DIS (mean±SD -0.30±1.28), DMS (mean±SD -0.45±1.37), EMA (mean±SD 0.25±1.33). The change in DIS and DMS severity over time did not differ across subtypes ($F(1, 211) < 2.42, p > 0.12$). The change in EMA differed across subtypes ($F(1, 211) = 4.46, p = 0.04$), with the largest decrease for subtype 1 (mean±SD -0.60±1.63) and a marginal increase for subtype 5 (mean±SD 0.09±0.84), but post-hoc pairwise comparisons did not reach significance after Bonferroni correction (all $p > 0.28$).

A.1.3 *Latent Transition Analysis*

Latent Transition Analysis (LTA; also called a latent Markov model) is a longitudinal extension of latent class analysis to model the latent class-membership over time. In this model, the subtype of a participant can change over time. The model estimates a *transition probability* to switch from one subtype to another over time. All characteristics were entered as continuous and the LTA model was estimated using Latent GOLD, starting with an Expectation-Maximization algorithm and switching to Newton-Raphson when close to the final solution. All he Default settings of Latent GOLD were used except for an increase in the number of random initial parameter sets from 16 to 100, in order to better avoid local minima.

A.1.4 *Online implementation of the Duke Structured Interview for Sleep Disorders*

We used an online implementation of the Duke Structured Interview for Sleep Disorders (DSISD) [9] to assess current comorbid (i) sleep disorders according to the ICSD-3 [10], (ii) diagnoses according to the main disease categories of the 10th revision of the International Statistical Classification of Diseases and Related Health Problems (ICD-10) [11], and (iii) mental and behavioral disorders according to the ICD-10 'Mental and behavioral disorders'-subcategories where insomnia is most common [12,13]. For each ICD-10 main category and the subdivided mental health categories, the DSISD shows participants the category name with some examples and asks whether a physician or specialist diagnosed a health problem of that category either currently (the past month) or in the past. If so, participants are asked to write down which ones. This text was mined for the mood disorder category to discriminate MDD from bipolar disorder. The DSISD was complemented by the four diagnostic criteria for RLS as defined by the International RLS Study Group (IRLSSG) [14] and with the Berlin Questionnaire [15] to estimate possible Obstructive Sleep Apnea.

A.2 SUPPLEMENTARY RESULTS

A.2.1 *Subtype differences in development etiology of dominant sleep complaints*

METHODS Of the 2,098 controls and 1,046 probable ID cases, 1,820 filled out the sleep history questionnaire (1,024 controls and 796 probable ID cases). The ID cases (mean $\pm$ SD age 52.5 ± 12.9 years, 79% female) belonged to subtypes 1-5 respectively: 19%, 30%, 16%, 21%, 14%. We investigated whether subtypes differed with respect to lifetime developmental course of first experiencing each of the three major sleep complaints of insomnia: difficulties initiating sleep (DIS), difficulties maintaining sleep (DMS), and early morning awakening (EMA). As part of a dedicated NSR sleep history questionnaire [13], participants were asked retrospectively if they had any recall of experiencing these three symptoms across each of the age ranges: 0-5, 6-12, 13-20, 21-30 , 31-40, 41-50, 51-60, 60+ years, up to their current age category. The retrospective methodology has been used successfully in studies on depression and sleep [16,17].

RESULTS The age category 13-20 years includes responses of all 1,820 participants. For later age categories, responses were only included if people were halfway the age category. (e.g., $\geq$25.5 for 21-30 years), resulting in the following number of available responses: 1,727 (21-30 years), 1,543 (31-40 years), 1,284 (41-50 years), 841 (51-60 years) and 297 (60+ years). Figure 3.4 A (chapter 3) shows, for controls and each of the five subtypes, the percentage of participants recalling any DIS, DMS and EMA in each age category. With few exceptions, recall of experiencing the symptoms increases with age category.

For the DIS trajectories, there is resemblance between type 1 and 2, who are most likely to experience difficulties initiating sleep already early in life. The groups of subtypes 4 and 5 are three times as old before they reach a similar prevalence. Subtype 3 is in between. DIS recall trajectories diverge most at 31-40 years. As compared to DIS, participants tend to recall slightly less DMS at earlier ages, but more at later ages. For the DMS trajectories, there is again resemblance between type 1 and 2, but now type 4 recall develops about the same as type 3 recall, and develops slower in type 5. DMS recall trajectories diverge most at 31-40 years. For the EMA trajectories, type 1, 2 and 4 develop highly similar, recall develops slowest in type 5, and type 3 is in between. EMA recall trajectories diverge most at 41-50 years. Because the between-subtype resemblance of trajectories group differently for the three complaints, a generalized recall bias is unlikely.

CONCLUSION In summary, the findings indicate that in spite of similarity of current sleep complaints (chapter 3, table 3.1), subtypes differ strongly with respect to the developmental course of experiencing each of the three major sleep complaints of insomnia. Complaint prevalence can be highly similar at some ages yet highly divergent at other ages.

A.2.2 *Treatment response differences between subtypes*

A.2.2.1 *Subtypes differ in their response to incidental benzodiazepine intake*

METHODS Participants (N=112, mean±SD age 56.6±11.2 years, 76% female) fulfilled the ISI $\geq$ 10 criterion for probable ID in community samples (ISI mean±SD 16.7±4.3). They were subtyped using the ITQ (percentage of subtypes 1-5 respectively: 33%, 37%, 17%, 12%, 13%) and asked to rate online how the incidental use of any benzodiazepine during the preceding night affected difficulties initiating sleep, difficulties maintaining sleep, early morning awakening and current fatigue relative to their usual complaints. Individuals differed with respect to the specific benzodiazepine prescribed by their general practitioner. Each of the four questions was answered on a Likert-type 5-point bipolar scale with zero indicating complaints as usual. Subtype differences in the effects experienced were evaluated with a multivariate general linear model including age as covariate.

RESULTS The overall multivariate test ($F(16, 406) = 1.751, p = 0.036$) indicated that subtypes provided a significantly different profile of ratings, shown in Figure 3.4 (chapter 3). In general, subtype 3 showed only marginal responses. Posthoc tests and pairwise comparisons found a lack of improvement in wake after sleep onset in subtype 3, which reached significance in comparison to the favorable effects experienced by subtype 4 ($p = 0.007$) and subtype 2 ($p = 0.042$). The favorable effects experienced by subtype 4 on wake after sleep onset and sleep onset latency (left panel, nonsignificant) were counterbalanced by no

effect on final wake time and the strongest adverse effect on next day's fatigue, which reached significance in comparison to subtype 1 ($p = 0.002$) and subtype 3 ($p = 0.015$).

CONCLUSION The findings support the clinical relevance of subtypes by showing differential subjectively experienced effects of benzodiazepines on major insomnia complaints.

A.2.2.2 *Subtypes differ in their response to cognitive behavioral therapy for insomnia disorder*

METHODS Subtypes may also differ with respect to effectiveness of cognitive-behavioral therapy for insomnia (CBTI). To investigate this possibility, we used the ITQ to subtype people that filled out the Insomnia Severity Index (ISI) before and after online CBTI or a waitlist condition. Insufficient data were available for subtypes 1, 3 and 5. Reasonable group sizes were available for subtype 2 (N=43, mean±SD age 50.8±12.9 years, 88% females, 26 treated, 17 waitlist controls) and subtype 4 (N=25, mean±SD age 53.2±9.8 years, 96% females, 16 treated, 9 waitlist controls).

RESULTS As compared to waitlist control, CBTI induced a strong decrease in insomnia severity (ISI) in subtype 2 (-5.5±7.8 mean±SD, $p < 0.001$, relative to a 29-point range) and a reasonable decrease in insomnia severity in subtype 4 (-3.1±7.3 mean±SD, $p = 0.003$). We subsequently evaluated whether specific insomnia severity symptoms were involved in the marginally significant treatment response difference between subtypes ($p = 0.08$). In subtype 2, as compared to waitlist control, CBTI induced a significant decrease in difficulties initiating sleep (-0.8±1.9 mean±SD, $p < 0.001$, relative to a range of 5 points). This improvement differed significantly ($p = 0.03$) from the effect of CBTI in subtype 4 where it induced a nonsignificant worsening of difficulties initiating sleep (0.1±1.5 mean±SD, $p = 0.69$).

CONCLUSION The findings support the clinical relevance of subtyping in understanding individual differences in treatment response.

A.2.3 *Conducting LCA in controls*

A.2.3.1 *Subtyping in controls*

A fundamental question is whether a similar classification could be made in the control group. To address this question, we have performed an LCA for bottom-up subtyping with the 19 ITQ characteristics assessed in the large sample of controls we had access to (N=2098). Heterogeneity among controls was best captured in six subtypes, rather than the five we consistently found in ID. To investigate whether some of these identified subtypes for controls would

overlap with the subtypes we found among ID, we calculated control subtype means for all characteristics. If a control subtype would match an ID subtype, its profile of group means should consistently (for 95% of the group means) fall within the 95% confidence interval of the corresponding group means of that ID subtype. The table below shows that this is not at all the case. For all 'control subtype' to 'insomnia subtype' comparisons, control subtype group means typically fall within a median of 2 insomnia subtype group means, and at most in 4, out of the 19 characteristics. The findings clearly indicate that classification of controls is fundamentally different from classification of ID.

Table: Counts of the number of times that control subtype group means fall within the 95% confidence of the insomnia subtype group means on the 19 ITQ characteristics. If a control subtype would be similar to an insomnia subtype, close to 19 of the control subtype group means would be expected to fall within the 95% confidence interval of the corresponding insomnia subtype group means.

Insomnia subtype	**1**	**2**	**3**	**4**	**5**
Control subtype					
1	3	3	3	2	2
2	0	0	1	4	2
3	2	2	3	0	2
4	0	2	0	1	1
5	2	1	0	3	4
6	0	2	0	2	4

A.2.3.2 *Clinical differences between subtypes of controls*

Although these findings indicate insomnia-specific subtyping, we also evaluated whether the associations of subtypes with depression and ERPs are specific to insomnia subtypes. For depression, we evaluated which of the six control subtypes had the highest lifetime and current risk of depression, shown in the table below. This was control subtype 5, with a current risk of 11.4% and a lifetime risk of 30.9%.

Table: Prevalence of lifetime depression and current mood disorder (F30-F39 ICD-10 category) in different control subtypes.

	Control subtype 1	Control subtype 2	Control subtype 3	Control subtype 4	Control subtype 5	Control subtype 6
N controls[a]	214	195	171	159	123	85
Mood (F30-F39)	$12^{2,3,4,5,6}$	$0^{1,3,5}$	$3^{1,2,4,5,6}$	$1^{1,3,5}$	$14^{1,2,3,4,6}$	$0^{1,3,5}$
	(5·6%)	(0·0%)	(1·8%)	(0·6%)	(11·4%)	(0·0%)
Lifetime depression	$29^{2,4,5,6}$	$11^{1,3,5}$	$32^{2,4,5,6}$	$8^{1,3,5}$	$38^{1,2,3,4,6}$	$2^{1,3,5}$
	(13·6%)	(5·6%)	(18·7%)	(5·0%)	(30·9%)	(2·4%)

[a] Control participants that completed the online structured interview modules and who were subtyped.
Note. Uppercase numbers indicate significant differences after Bonferroni correction.

As can be retrieved from the table above, only 2 group means out of the 19 ITQ characteristics of control subtype 5 fell within the 95% group mean confidence intervals of the insomnia subtype (1) with the highest lifetime and current risk of depression. The characteristic group means of the high-risk control subtype 5 overlapped more, but still marginal, with those of ID subtypes 4 and 5 (3 and 4 times, respectively), which had in fact the lowest risks of current (0.5% and 2.3%) and lifetime (8.2% and 13.1%) depression. The findings indicate that the control subtype with the highest current and lifetime risk of depression does not at all resemble the ID subtype with the highest current and lifetime risk of depression.

Finally, with respect to ERPs, sufficient controls were available in our ERP study to generate group mean curves for control subtypes 1, 2 and 6. In contrast to the specific and significant difference we found for insomnia subtype 4, the cluster-based random permutation tests did not find any significant control subtype difference anywhere along their ERP-curves. Although we cannot exclude the possibility that other control subtypes, not sufficiently represented in our sample, could still show the deviating profile we have discovered in insomnia subtype 4, the finding at least indicates that it is not trivial to find subtype differences in ERPs and suggests insomnia-specific relevance of the deviating curves we found in insomnia subtype 4. The ERPs of controls are shown in the Figure below.

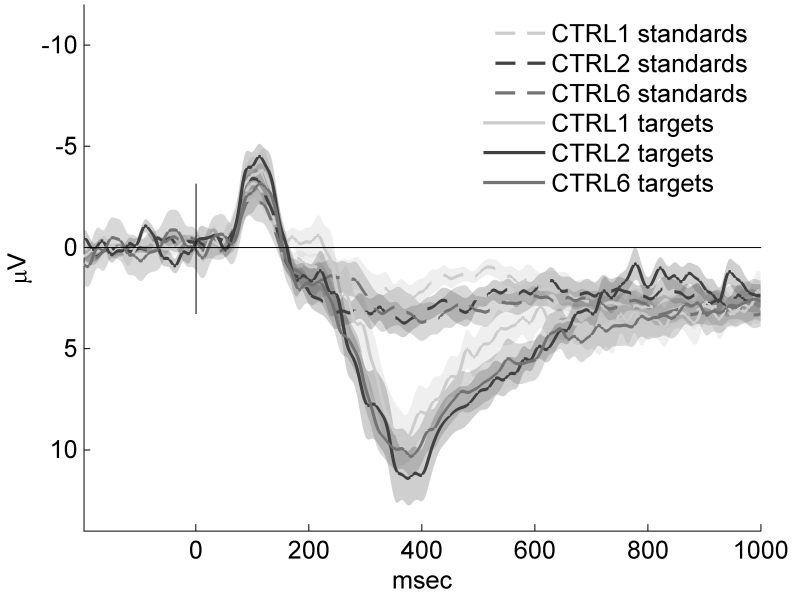

Figure: Auditory event related potentials for standard tones (dashed lines) and deviant tones (solid lines) recorded during an oddball task do not differ between three control subtypes. None of the subtype shows the profile of enhanced P300 and systematic Late Positive Potential responses on standard tones that characterized insomnia subtype 4. Shaded areas indicate standard error.

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A.3 SUPPLEMENTARY FIGURES

A1 Overview of questionnaires, characteristics, and items.

A2 Analysis scheme to develop and validate subtype model.

A3 Analysis scheme to assess clinical relevance of the subtypes.

A4 Complete multivariate profile plot.

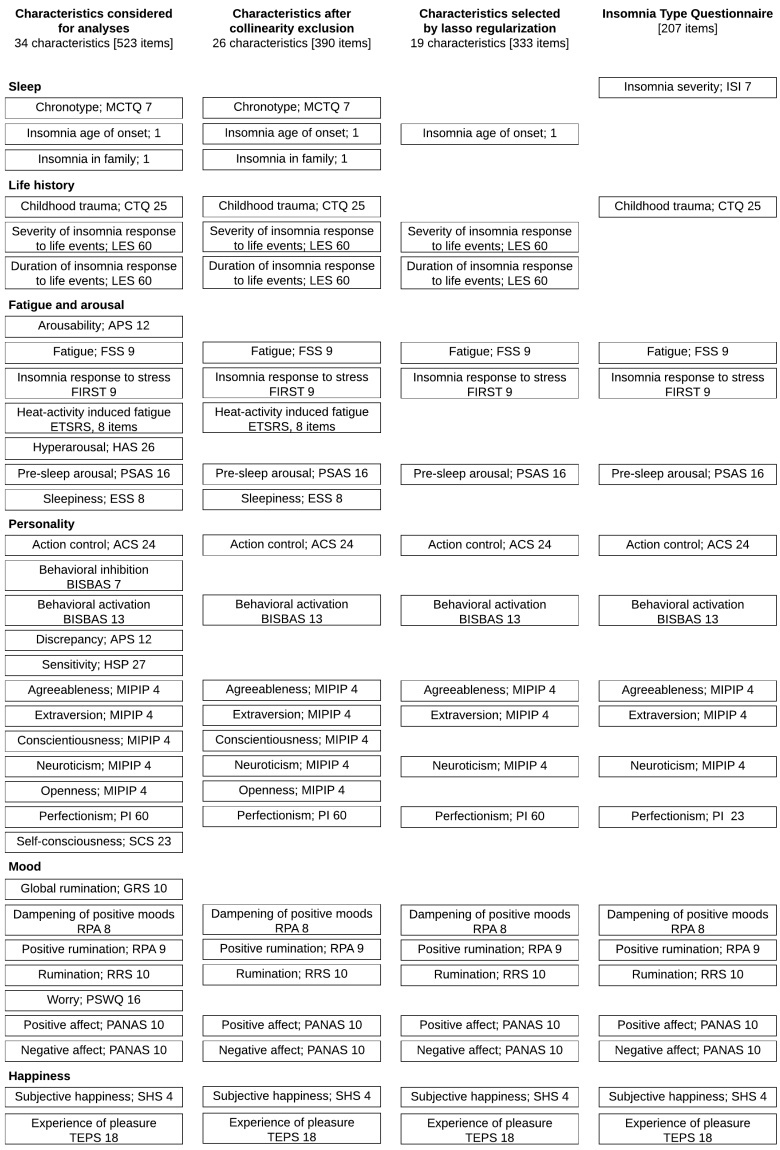

Figure A.1: Overview of questionnaires, characteristics, and items. (continues on next page)

Figure A.1: Chart showing the different characteristics, corresponding questionnaire (abbreviation), and number of items in each part of the analyses. For the analyses, we computed the total score for each characteristic, by summing all its items. We first considered 34 characteristics for the analyses (first column). Second, to prevent multicollinearity problems, we stepwise selected from highly correlated characteristics ($r = 0.70$ first, steps of -0.05) only the one with the lowest median correlation with all other characteristics. We stopped when the strongest correlation ($r = 0.53$) was between two characteristics reflecting different domains (pre-sleep arousal and negative affect), preserving 26 characteristics for subsequent analyses (second column). Third, in order to create a concise questionnaire, the Insomnia Type Questionnaire, we used regression with lasso regularization to select the most discriminating characteristics, resulting in a selection of 19 characteristics (third column). Finally, to reduce the number of selected items and ascertain high test-retest reliability, we replaced the LES for the CTQ, limited the number of questions for the PI, and omitted the insomnia age of onset, as many participants reported this to be difficult to estimate (details in Supplementary Methods A.1.2.2), resulting in 17 characteristics (fourth column). Abbreviations: MCTQ = Munich Chronotype Questionnaire; CTQ = Childhood Trauma Questionnaire; LES = Life Experiences Survey; APS = Arousal Predisposition Scale; FSS = Fatigue Severity Scale; FIRST = Ford Insomnia Response to Stress Test; ETSRS = Experienced Temperature Sensitivity and Regulation Survey; HAS = Hyper Arousal Scale; PSAS = Pre-Sleep Arousal Scale; ESS = Epworth Sleepiness Scale; ACS = Action Control Scale; BISBAS = Behavioral Inhibition/Activation Scale; APS = Almost Perfect Scale; HSP = Highly Sensitive Person test; MIPIP = Mini-IPIP; PI = Perfectionism Inventory; SCS = Self-Consciousness Scale; GRS = Global Rumination Scale; RPA = Response to Positive Affect; RRS = Ruminative Response Scale; PSWQ = Penn State Worry Questionnaire; SHS = Subjective Happiness Scale; TEPS = Temporal Experience of Pleasure Scale.

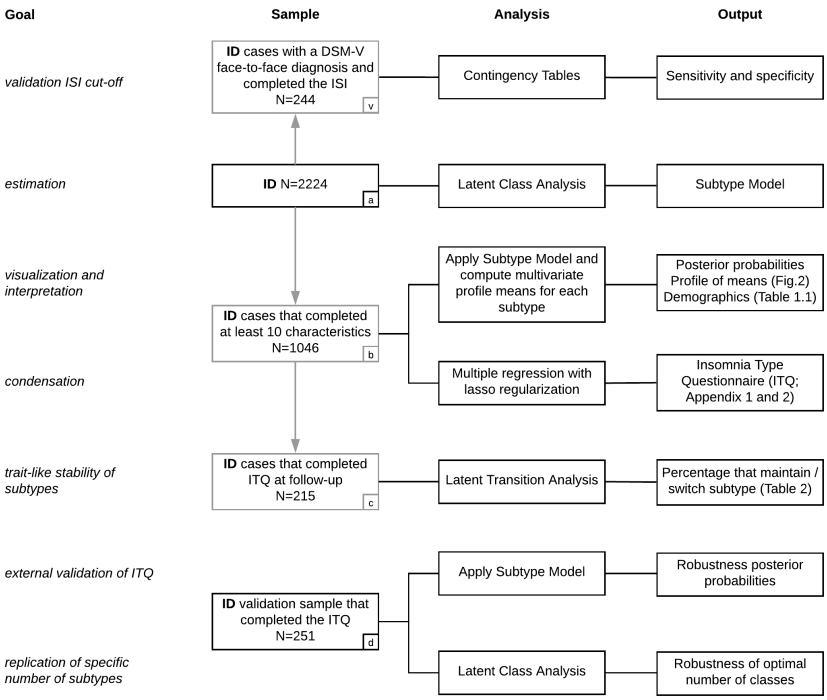

Figure A.2: Analysis scheme to identify and validate subtypes. The scheme shows the goals, (sub)samples, analyses, and outputs of all steps involved in finding subtypes. Derived samples represent the people that still participated in the NSR and responded to emailed newsletters with invitations for further participation. No inclusion- or exclusion criteria other than initial selection for the ID or control group were applied. The subsample (b) that completed at least 10 characteristics and was selected for interpretation, did not differ from the complete sample (a) that was used to estimate the subtype model on any of the characteristics (t-tests, all p>0·09). The different samples did not differ in age (all $p > 0.44$) or sex (all $\chi^2(1) < 1.15$, all $p > 0.28$).

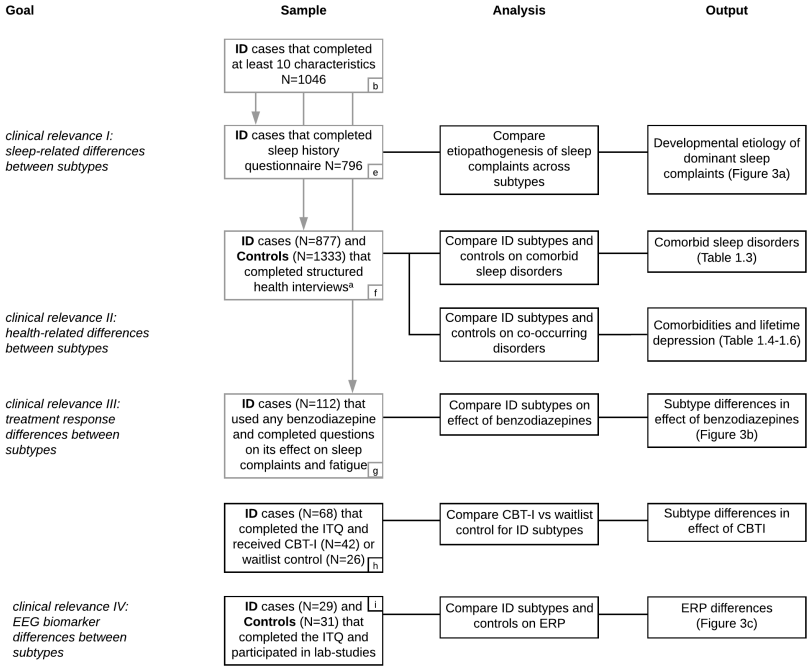

Figure A.3: The scheme shows the goals, (sub)samples, analyses steps, and outputs of each of the assessments of clinical relevance of subtyping. (continues on next page)

Figure A.3: Subsamples (i.e. derived from the larger sample) are indicated by an arrow and grey (instead of black) outlined boxes. For samples b-g no inclusion- or exclusion criteria were applied other than initial selection for the ID or control group. The derived samples e-g represent the people that still participated in the NSR and responded to emailed newsletters with invitations for further participation. Independent sample h included participants with an age between 18 and 70 years and a diagnosis of ID according to ICSD3 and DSM-5 assessed in a face-to-face interview. Exclusion criteria were a comorbid psychiatric or neurological condition, shift-work and daily use of sleep medication. Independent sample i included participants with an age between 18 and 70 years and a diagnosis of ID according to ICSD3 and DSM-5, and age- and sex-matched controls without sleep difficulties, both assessed in a face-to-face interview. Exclusion criteria were diagnosed sleep apnea, restless legs syndrome, or other somatic, neurological or psychiatric conditions; use of sleep medication within the last 2 months; and shifted or irregular sleep-wake rhythms assessed using one week of actigraphy. Most of the ID (sub)samples did not differ in age (all $p > 0\Delta 31$) or sex (all $p > 0.67$) from the overall sample, except for sample g, which was, on average somewhat older (56.6 ± 11.2) than the overall sample (51.1 ± 13.7 years; $t(142.5) = 2.3, p = 0.02$), and sample h, which consisted of more women (91%) than the total sample (78% female; $\chi^2(1) = 5.8, p = 0.02$).
[a] The online structured interviews assessed sleep disorders according to the ICSD3, disease diagnoses according to the main disease categories of the 10th revision of the International Statistical Classification of Diseases and Related Health Problems (ICD-10) [1,2], and more in detail the mental and behavioral disorders according to the ICD-10 'Mental and behavioral disorders'. More information on the online structured interviews is given in the Supplementary Methods A.1.4.

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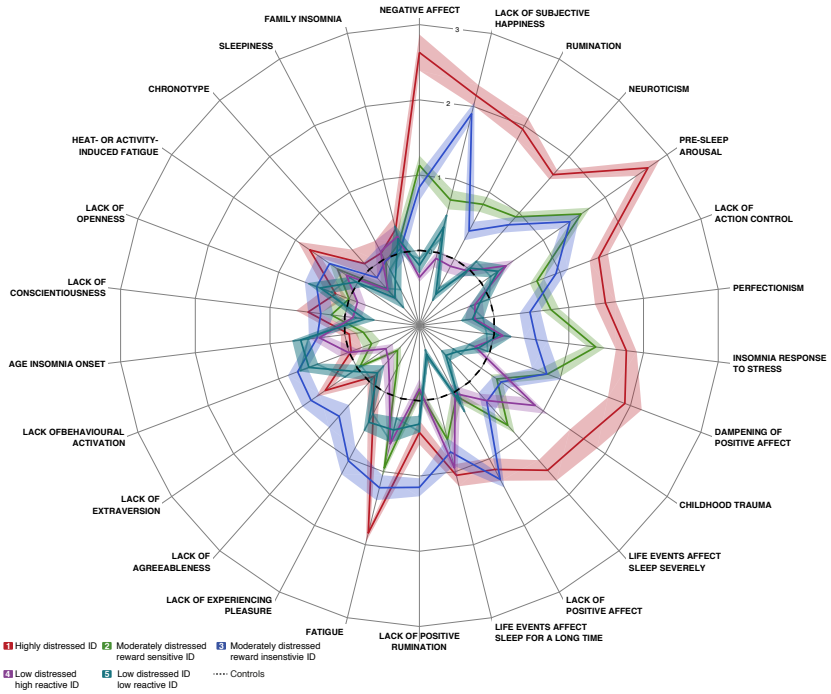

Figure A.4: Profile plot showing scaled subtype group means (z-scores standardized to mean and standard deviation of controls) on the 26 characteristics. Characteristics are ordered clockwise according to the proportion of variance accounted for by the five subtypes. Positive characteristics (e.g. well-being) were reverse coded and renamed (e.g., lack of well-being) such that higher values indicate higher general distress for all characteristics.

A.4 SUPPLEMENTARY TABLES

A1 Examples of heritability of considered characteristics.

A2 Examples of gene variants associated with considered characteristics.

A3 Examples of brain structural correlates of considered characteristics.

A4 Questionnaires considered for analyses.

A5 Mean scores on the 26 characteristics for controls, all participants with probable ID, and each of the five ID subtypes.

A6 Goodness of fit-statistics for 1-6 latent class models.

A7 Classification statistics of 5-class model.

A8 Typification of ID subtypes.

Table A.1: Examples of heritability of considered characteristics.

Characteristic	h^2	Reference
Sleep		
Chronotype	0·38-0·48	(Von Schantz et al., 2015)
Insomnia age of onset	NA	
Insomnia diagnosis	0·22-0·59	(Lind et al., 2015)
Insomnia in family	NA	
Life history		
Childhood trauma	NA	
Severity and duration of insomnia response to life events	NA	
Fatigue and arousal		
Fatigue (tiredness)	0·06-0·50	(Deary et al., 2017)
Heat/activity-induced fatigue		
Hyperarousal	NA	
Insomnia response to stress	0·24-0·43	(Drake et al., 2011)* (Fernandez-Mendoza et al., 2014)*
Sleepiness	0·29-0·38	(Carmelli et al., 2001)* (Watson et al., 2006) (Gottlieb et al., 2007)* (Lessov-Schlaggar et al., 2008)*
Personality		
Action control	0·52	(Gustavson et al., 2014)*
Behavioral activation	0·28-0·35	(Takahashi et al., 2010)
Agreeableness	0·35	(meta-analysis: Vukasović et al., 2015)
Conscientiousness	0·31	(meta-analysis: Vukasović et al., 2015)
Extraversion	0·36	(meta-analysis: Vukasović et al., 2015)
Neuroticism	0·37	(meta-analysis: Vukasović et al., 2015)
Openness	0·41	(meta-analysis: Vukasović et al., 2015)
Perfectionism	0·23-0·42	(Wade et al., 2007, Iranzo-Tatay et al., 2015)
Mood		
Dampening of positive moods	NA	
Negative affect	0·47-0·53	(Mikolajewski et al., 2013)* (Zheng et al., 2016)*
Positive affect	0·59	(Boardman et al., 2008)
Rumination	0·37-0·41	(Johnson et al., 2014)*
Brooding	0·21	(Moore et al., 2013)*
Happiness		
Positive rumination	NA	
Subjective happiness / Psychological well-being	0·36-0·64	(Gigantesco et al., 2011) (Gatt et al., 2014) (Bartels, 2015)† (Nes et al., 2015)†
Experiencing pleasure	NA	

Note. Information in this table provides examples and may not include all literature available on the characteristics. NA indicates non-available estimates.
h^2 represents the heritability estimate.
* Using the same questionnaire as included in the current study.
† Meta-analysis included studies that used the same questionnaire.

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Table A.2: Examples of gene variants associated with considered characteristics.

Characteristic	SNP/region	Chr	Gene	Reference
Sleep				
Chronotype			PER2, RGS16, FBXL13, AK5	(Kalmbach et al., 2017)
Insomnia age of onset	NA	NA	NA	
Insomnia diagnosis		17	SLC6A4	(Deuschle et al., 2010)
			MEIS1, MED27, HHEX, RHCG, IPO7, TSNARE1,	(Hammerschlag et al., 2017)
			MEIS1, CYCL1, TGFBI, WDR27, TMEM132E	(Lane et al., 2017)
Insomnia in family	NA	NA	NA	
Life history				
Childhood trauma	rs1360780	6	FKBP5	(Klengel et al., 2013)*
	(4 SNPs)	6	FKBP5	(Watkins et al., 2016)
	rs7305115	12	TPH2	(Pearson et al., 2014)*
	rs6311	13	HTR2A	
	rs6295	5	HTR1A	
		17	SLC6A4	(Walsh et al., 2014)*
Severity and duration of insomnia response to life events	NA	NA	NA	
Fatigue and arousal				
Fatigue		X	MAOA-uVNTR	(Choi-Kwon et al., 2017)*
	rs4719714	7	IL-6	(Miaskowski et al., 2010)
			TNFα, IL1b, IL4, IL6, HLS, IFN-γ, 5-HT & NR3C1	(Wang et al., 2017)[c]
			DRD2, PRRC2C, C3orf84, ANO10 & ASXL3	(Deary et al., 2017)
Heat/activity-induced fatigue	NA	NA	NA	
Hyperarousal	rs2267735		ADCYAP1R1	(Ressler et al., 2011, Jovanovic et al., 2012)
	(4 SNPs)	6	FKBP5	(Watkins et al., 2016)
		17	SLC6A4	(Walsh et al., 2014, Sayin et al., 2010)
		22	ADORA2A	(Hohoff et al., 2010)
Insomnia response to stress	NA	NA	NA	
Sleepiness	rs1823068	5	PDE4D	(Gottlieb et al., 2007)*
Personality				
Action control	NA	NA	NA	
Behavioral activation	rs7305115	12	TPH2	(Pearson et al., 2014)*
	rs6311	13	HTR2A	
	rs6295	5	HTR1A	
			DRD2 x COMT interaction	(Reuter et al., 2005)
Reward Responsiveness		6	OPRM1	(Johnson et al., 2016)*
Agreeableness	rs806366	6	CNR1	(Juhasz et al., 2009)†

Table A.2: (continued)

Conscientiousness	rs2576037	18	KATNAL2 (intron)	(de Moor et al., 2012)†
Extraversion		2	LOC101928162	(van den Berg et al., 2016)†
	rs57590327	3	GBE1 (intergenic)	(Lo et al., 2017)†
	rs2164273	8	MTMR9 (intron)	
	rs6481128	10	PCDH15 (intergenic)	
	rs1426371	12	WSCD2 (intron)	
Neuroticism	136 loci		599, max gene-set neurogenesis	(Nagel et al., 2017)†
		8	XKR6 (intergenic)	(Lo et al., 2017)†
		22	L3MBTL2 (exon) / CHADL (intron)	
	rs806366	6	CNR1	(Juhasz et al., 2009)†
Openness	rs1477268 and rs2032794	5	RASA1 (intergenic)	(de Moor et al., 2012)†
	rs677035	11	KCNJ1	(Janssens et al., 2012)†
Perfectionism	rs4570625	12	TPH2	(Di Nocera et al., 2014)
	Taq1A	11	DRD2	
	rs6280	3	DRD3	
		11	DRD4	(Bachner-Melman et al., 2007)
		11	IGF2	
		12	AVPR1a	
Mood				
Dampening of positive moods	NA	NA	NA	
Negative affect	rs16969968	15	CHRNA5/A3/B4	(Chen et al., 2015)*
	rs588765			
Positive affect	rs322931	1	LINC01221:miR-181a/b	(Wingo et al., 2017)*
	rs7550394			
Rumination	rs6265	11	BDNF	(Hilt et al., 2007) (Stone et al., 2013)*
			BDNF	(Beevers et al., 2009)*
	rs740603	22	COMT	(Pap et al., 2012)*
	rs464316			
Happiness				
Positive rumination	NA	NA	NA	
Subjective happiness	rs3756290	5	RAPGEF6	(Okbay et al., 2016)
	rs2075677	20	CSE1L	
	rs4958581	5	NMUR2	
Experiencing pleasure	NA	NA	NA	

Note. Information in this table provides examples and may not include all literature available on the characteristics. NA indicates non-available data.
Abbreviations: SNP = single-nucleotide polymorphism; Chr = cell cycle genes homology region.
* Using the same questionnaire as included in the current study.
† Using questionnaire based on the Five Factor Model of Personality, similar to the Mini-IPIP that was used in the current study.

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Table A.3: Examples of brain structural correlates of considered characteristics.

Characteristic	Brain region	Metric	Direction	Reference
Sleep				
Chronotype	Precuneus, posterior parietal cortex	GMD	Negative association with morningness	(Takeuchi et al., 2015)
	Bilateral orbitofrontal cortex	GMD	Positive association with morningness	
Insomnia age of onset	NA			
Insomnia diagnosis	Several cortical areas, but variable			(reviewed in: van Someren et al., 2013)
Insomnia in family				
Life history				
Childhood trauma	Right hippocampus, Right dorsolateral prefrontal cortex	GMV	Negative association	(Paquola et al., 2016)†
Sensitivity to negative life events	Ventrolateral prefrontal cortex (VLPFC)	GMV	Positive association	(Qiao et al., 2013)
Severity and duration of insomnia response to life events	NA			
Fatigue and arousal				
Fatigue	Thalamus, Pallidum, Superior cerebellar peduncle	GMV	Negative association	(MS patients: Bernitsas et al., 2017)*
Heat/activity-induced fatigue	NA			
Hyperarousal	NA			
Insomnia response to stress	NA			
Sleepiness	Bilateral OFC	GMV	Negative association	(Shi et al., 2017)*
Personality				
Action control	NA			
Behavioral activation	Ventromedial prefrontal cortex (vmPFC), Inferior parietal lobule (IPL)	GMV	Positive association (females), negative association (males)	(Li et al., 2014)*
Agreeableness	Prefrontal cortex	SBM	Thinner cortex	(Riccelli et al., 2017)
	Fusiform gyrus	SBM	Smaller area	(Riccelli et al., 2017)
Conscientiousness	Prefrontal regions	SBM	Thicker cortex, smaller area and folding	(Riccelli et al., 2017)
Extraversion	Bilateral amygdala, Bilateral parahippocampal gyrus, Right middle temporal gyrus, Left superior frontal gyrus	GMV	Negative association	(Lu et al., 2014)

Table A.3: (continued)

	Precuneus	SBM	Thicker cortex	(Riccelli et al., 2017)
	Superior temporal cortex	SBM	Smaller area	(Riccelli et al., 2017)
Neuroticism	Right cerebellum	GMV	Positive association	(Lu et al., 2014)
	Left superior frontal gyrus	GMV	Negative association	(Lu et al., 2014)
	Prefrontal-temporal regions	SBM	Thicker cortex, smaller area and folding	(Riccelli et al., 2017)
Openness	Prefrontal-parietal	SBM	Thinner cortex, greater area and folding	(Riccelli et al., 2017)
Perfectionism	Anterior Cingulate Cortex	GMV	Positive association	(Wu et al., 2017)
Mood				
Dampening of positive moods	NA			
Negative affect	Left amygdala	GMV	Negative association	(Dennison et al., 2015)*
Positive affect	Right caudate	GMV	Volume reduction over time was predicted by positive affect	(Dennison et al., 2015)*
	Hippocampus	GMV	Positive association	(Dennison et al., 2015)*
Rumination	Dorsolateral prefrontal cortex (DLPFC), Parahippocampal gyrus (PHG)	GMV	Positive association	(Wang et al., 2015)[a]
Happiness				
Life satisfaction	Parahippocampal gyrus (PHG)	GMV	Positive association	(Kong et al., 2014)
	Left precuneus, Left ventromedial prefrontal cortex	GMV	Negative association	
Positive rumination	NA			
Subjective happiness	Rostral anterior cingulate cortex (rACC)	GMD	Positive association	(Matsunaga et al., 2016)*
	Right precuneus	GMV	Positive association	(Sato et al., 2015)*
Experiencing pleasure	NA			

Note. Information in this table provides examples and may not include all literature available on the characteristics. NA indicates non-available data.
Abbreviations: GMV = gay matter volume; GMD = gray matter density; SBM = surface-based morphometry indices (i.e., cortical thickness, surface area, cortical folding, or any combination); MS = Multiple Sclerosis patiets.
* Using the same questionnaire as included in the current study.
[a] Used the Chinese Short Ruminative Responses Scale (SRRS), which is based on the Ruminative Response Scale (used in the current study). † Meta-analysis included studies that used the same questionnaire.

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Table A.4: Questionnaires considered for analyses.

Questionnaire	Description	Items [range]
Sleep		
Munich Chronotype Questionnaire[1†]	Measures temporal organization.	7 [1 – 7]
Insomnia age of onset†	Age participant indicated to first suffer from insomnia (DSM-V criteria: sleep problems for at least three nights a week for at least three months).	
Insomnia in family†	Question whether family members suffer from insomnia.	
Life history		
Childhood Trauma Questionnaire[2†]	Measures five forms of childhood adversity: physical, emotional and sexual abuse; and physical and emotional neglect.	25 [1 – 5]
LONGSCAN adaptation of Life Experiences Survey[3]		
Severity of insomnia response to life events†	Proportion of experienced life events that made someone sleep worse or much worse (worst 2 of 7-point Likert-type scale).	0 – 1
Duration of insomnia response to life events†	Proportion of experienced life events that affected someone's sleep for at least one month (longest 5 of 9-point Likert-type scale).	0 – 1
Fatigue and arousal		
Arousal Predisposition Scale[4]	Measures arousability as a predispostion or a trait.	12 [1 – 5]
Fatigue Severity Scale[5†]	Measures disabling fatigue.	9 [1 – 4]
Ford Insomnia Response to Stress Test[6†]	Measures the stress-related vulnerability for sleep disturbance in response to commonly experienced stressful situations.	9 [1 – 4]
Heat/activity-induced fatigue[7†]	Measures the effect of a warm environment or physical exertion on fatigue.	8
Hyper Arousal Scale[8]	Measures hyperarousal behavioral traits.	26 [0 – 3]
Pre-Sleep Arousal Scale[9†]	Measures the somatic and cognitive manifestations of arousal when falling asleep.	8 [1 – 5]
Epworth Sleepiness Scale[10†]	Measures daytime sleepiness.	8 [0 – 4]
Personality		
Action Control Scale[11†]	Measures an individual's response tendency: i.e., the extent to which an individual is decisive and takes control over their behavior.	24 [0 – 1]
Behavioral Inhibition/ Activation Scale[12]	Measures the motivational system.	
Behavioral inhibition scale	Measures threat sensitivity.	7 [1 – 4]
Behavioral activation scale†	Measures reward sensitivity.	13 [1 – 4]
Almost Perfect Scale[13]		
Discrepancy	Measures the negative aspect of perfectionism.	12 [1 – 5]
Highly Sensitive Person test[14]	Measures sensory-processing sensitivity.	27 [0 – 7]
Mini-IPIP[15]	Measures the Big-Five personality factors.	
Agreeableness†	Big-Five personality factor related to sensitivity, compassion and understanding.	4 [1 – 5]
Conscientiousness†	Big-Five personality factor related to being organized and proactive.	4 [1 – 5]
Extraversion†	Big-Five personality factor related to being talkative, outgoing and communicative.	4 [1 – 5]
Neuroticism†	Big-Five personality factor related to worrying.	4 [1 – 5]

Table A.4: (continued)

Openness†	Big-Five personality factor related to being imaginative, creative and adaptive.	4 [1 – 5]
Perfectionism Inventory[16]†	Measures different aspects of perfectionism.	60 [1 – 5]
Self Consciousness Scale[17]	Measures private and public self-consciousness and social anxiety.	23 [0 – 4]
Mood		
Global Rumination Scale[18]	Measures general rumination.	10 [1 – 7]
Responses to Positive Affect[19]		
Dampening of positive moods†	Measures the tendency to decrease/ eliminate the positive mood.	8 [1 – 4]
Positive rumination†	Measures the tendency to maintain/ enhance positive moods.	9 [1 – 4]
Ruminative Response Scale[20]†	Measures brooding ("moody pondering") and reflection ("purposeful turning inwards").	10 [1 – 4]
Penn State Worry Questionnaire[21]	Measures general worry and rumination.	16 [1 – 5]
Positive and Negative Affect Scale[22]	Measures affect.	
Positive affect†	Measures the tendency of experiencing positive affect.	10 [1 – 5]
Negative affect†	Measures the tendency of experiencing negative affect.	10 [1 – 5]
Happiness		
Subjective Happiness Scale[23]†	Measures global subjective happiness.	4 [1 – 7]
Temporal Experience of Pleasure Scale[24]†	Measures anticipatory ("wanting") and consummatory ("liking") pleasure.	18 [1 – 6]

Note. Included information is based on the original versions of the questionnaires, see references. More detailed information on the implementation in the Sleep Registry can be found in the Supplementary material of [25]. The questionnaires considered for the analyses comprised 34 sum- scores and 513 items. Of these, we included 26 characteristics for the actual Latent Class Analysis, which together comprised 380 items.

† The 26 characteristics that were included in the Latent Class Analysis to estimate the subtype model.

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Table A.5: Mean scores on the 26 characteristics for controls, all participants with probable ID, and each of the five ID subtypes.

Characteristic	Controls (*N* = 2,098)	Insomnia (*N* = 2,224)	Effect (Cohen's *d*)	Subtype 1 (*N* = 200)	Subtype 2 (*N* = 323)	Subtype 3 (*N* = 153)	Subtype 4 (*N* = 209)	Subtype 5 (*N* = 161)
Sleep								
Chronotype	03:58	03:52	-0·08	03:44	03:43	04:10	03:35	03:56
Insomnia age of onset†	-	38·3	-	34·7	31·4	41·6	41·1	45·3
Insomnia in family	31%	39%	-	46%	37%	33%	41%	40%
Life history								
Childhood trauma†	37·8	43·3	0·41*	57·7	40·7	41.6	48·2	33·0
Severity of insomnia response to life events†	0·18	0·29	0·53*	0·46	0·32	0·24	0·24	0·10
Duration of insomnia response to life events†	0·26	0·42	0·54*	0·55	0·42	0·46	0·53	0·09
Fatigue and arousal								
Fatigue†	29·7	41·5	1·02*	49·7	40·0	42·9	36·4	34·4
Heat/activity-induced fatigue	0·13	0·38	0·34*	0·65	0·35	0·44	0·25	0·15
Insomnia response to stress†	17·5	22·4	0·81*	27·3	25·1	20·6	18·2	17·8
Pre-sleep arousal†	27·0	38·7	1·14*	50·2	40·9	39·3	30·4	29·3
Sleepiness	7·3	7·5	0·06	7·6	7·1	7·1	7·7	6·1
Personality								
Action control†	15·3	12·5	-0·56*	7·9	12·1	10·8	16·2	15·9
Agreeableness†	16·6	17·2	0·20*	16·9	18·2	15·0	17·7	17·1
Behavioral activation†	34·2	34·0	-0·03	34·3	36·0	30·2	34·1	31·0
Conscientiousness	14·8	14·4	-0·11	13·1	14·2	13·7	15·2	15·7
Extraversion†	12·7	12·3	-0·11	10·8	12·8	9·9	14·3	12·4
Neuroticism†	9·7	12·5	0·74*	16·2	13·3	12·8	9·6	9·8
Openness	15·1	14·6	-0·16	14·5	15·2	13·7	15·5	13·9
Perfectionism†	226·4	250·7	0·48*	298·3	262·8	249·5	213·7	212·6
Mood								
Dampening of positive moods†	10·5	12·3	0·56*	15·4	12·6	12·6	10·0	10·1
Negative affect†	14·5	18·9	0·70*	27·6	20·1	18·7	12·7	13·5
Positive affect†	32·8	29·5	-0·47*	24·8	32·4	23·8	32·7	31·6
Rumination†	17·6	20·8	0·57*	27·6	21·8	19·8	17·0	14·9
Happiness								
Positive rumination†	22·4	21·2	-0·23*	20·3	23·0	16·7	23·1	20·8
Subjective happiness†	22·5	18·1	-0·84*	12·6	19·2	13·8	22·8	20·9
Experiencing pleasure†	76·3	74·8	-0·16*	73·4	79·6	66·9	77·6	72·2

* Significant at α-level of 0.05, Bonferroni corrected for multiple testing.

† Characteristics selected by *lasso* regularization and/or for which $\geq$ 15% of variance in the characteristics was explained.

Table A.6: Goodness of fit-statistics for 1-6 latent class models.

	1 class model	2 class model	3 class model	4 class model	5 class model	6 class model
BIC	138212.3	135494.6	135069.9	134954.5	**134908.9**	134959.2
Number of Parameters	51	103	155	207	259	311
Classification error	0	0.13	0.21	0.25	0.28	0.31
Entropy R^2	1.00	0.61	0.57	0.57	0.56	0.56
R^2	1.00	0.65	0.57	0.54	0.53	0.50
Cluster sizes						
1	1	0.51	0.38	0.36	0.31	0.27
2	-	0.49	0.33	0.26	0.20	0.26
3	-	-	0.29	0.21	0.19	0.17
4	-	-	-	0.17	0.15	0.11
5	-	-	-	-	0.15	0.10
6	-	-	-	-	-	0.09

Note. $N = 2,224$. BIC = Bayesian Information Criterion.

Table A.7: Classification statistics of 5-class model.

1.1 *Five-class model classification statistics*

N	Class. Error[a]	R^2 [b]	Entropy R^2 [b]
1,046	0·13	0·76	0·79

1.2 *Class sizes and posterior probability distribution in each class*

	Class				
	1	2	3	4	5
N (%)	200 (19%)	323 (31%)	153 (15%)	209 (20%)	161 (15%)
Posterior probability[c]	0·99 (0·88-1·00)	0·93 (0·77-0·99)	0·91 (0·72-0·99)	0·96 (0·77-1·00)	0·95 (0·76-0·99)

[a] Classification error is the estimated proportion of misclassified cases.
[b] Standard and entropy R^2 indicate how well class-membership can be predicted based on the observed characteristics.
[c] Median (IQR) posterior probabilities of participants assigned to each class.

Table A.8: Typification of ID subtypes.

Insomnia Subtype	Demographics (average age, % female-male)	Description	Sleep complaints (DIS, DMS, EMA) and sleep duration	Sleep-related daytime dysfunction and worrying.
1: highly distressed	**50** years old; **20%** of females; **16%** of males.	Highly distressed across many characteristics, in particular negative moods, like *distressed* and *afraid*. Less happy than peers and never as happy as they might be. Experiences a lot arousal when trying to fall asleep.	**Mild** difficulty initiating sleep, **very severe** difficulty maintaining sleep and **very severe** early morning awakenings. Average sleep duration is **6:08** hours.	Sleep problems interfere **much** with daily life and cause **much** worry.
2: moderately distressed reward sensitive	**49** years old; **33%** of females; **23%** of males.	Difficulty sleeping in response to (or anticipation of) stressful events and heightened arousal when trying to fall asleep. This difficulty sleeping is not related to the experience of positivity: feels generally happy.	**Mild** difficulty initiating sleep, **very severe** difficulty maintaining sleep and **moderate** early morning awakenings. Average sleep duration is **6:07** hours.	Sleep problems interfere **somewhat** with daily life and cause **some** worry.
3: moderately distressed reward insensitive	**54** years old; **12%** of females; **23%** of males.	Moderately distressed, especially a pronounced lack of positivity: not very happy in general; little experiences of positive moods, including *excitement*; and little positive rumination.	**Mild** difficulty initiating sleep, **very severe** difficulty maintaining sleep and **mild** early morning awakenings. Average sleep duration is **5:58** hours.	Sleep problems interfere **much** with daily life and cause **some** worry.
4: low distressed high reactive	**54** years old; **22%** of females; **14%** of males.	Distress levels similar to controls, except for life history: more childhood trauma and a larger effect of life events on sleep than controls.	**Mild** difficulty initiating sleep, **very severe** difficulty maintaining sleep and **moderate** early morning awakenings. Average sleep duration is **5:47** hours.	Sleep problems interfere **somewhat** with daily life and cause **some** worry.
5: low distressed low reactive	**57** years old; **13%** of females; **24%** of males.	Experiences largely match those of controls. Exceptions are a relative lack of happiness and pleasure. Ruminates very little on both positive emotions and on distress.	**Mild** difficulty initiating sleep, **very severe** difficulty maintaining sleep and **moderate** early morning awakenings. Average sleep duration is **5:51** hours.	Sleep problems interfere **somewhat** with daily life and cause **some** worry.

Note. Sleep complaint qualifications show the model response for each class: none – mild – moderate – severe – very severe; not at all – a little – somewhat – much – very much (Insomnia Severity Index questions 1, 3, 5). For assessment of the described characteristics see Benjamins, Migliorati et al. (2017). DMS = difficulty maintaining sleep; EMA = early morning awakenings; DIS = difficulty initiating sleep.

A.5 FULL-LENGTH COMMENTARIES ON ORIGINAL PAPER

A.5.1 *Ferini-Strambi L, Fossati A, Sforza M, Galbiati A*

We read with great interest the Article by Tessa Blanken and colleagues [1], in which the authors aimed to identify subtypes of insomnia by means of data-driven analyses on the basis of several biologically based traits. This study is highly relevant since the conception of insomnia as a heterogeneous disease is gaining more and more credit, and might represent a cornerstone by promoting discoveries of new mechanisms and different treatments.

The measures used in latent class analyses by Blanken and colleagues for identifying insomnia subtypes were based exclusively on self-reported scores of sleep, life history, fatigue and arousal, personality, mood, and happiness. In our opinion, this method raises a major issue, because it makes it difficult to assess whether the authors accurately estimated the interrelationships between the observable indicators of the different constructs, or whether their findings were seriously biased by shared method variability. McCrae [2] showed that roughly 40% of the variance in self-reports and single informant ratings is due to method variance. Therefore, the use of multiple informants is needed for future research to reduce this issue [2].

The assessment of insomnia is an important topic because its diagnosis is currently based only on subjective criteria. However, in-depth clinical evaluation (assessed in the study by Blanken and colleagues [1] in a subsample of participants) and polysomnographic recording could be fundamental to revealing other pathological conditions, such as periodic limb movement disorder or sleep apnoea syndrome, in patients with a previous diagnosis of insomnia. Furthermore, the objective finding of short total sleep time characterises the most severe phenotype of insomnia [3]. In these patients, a higher cardiometabolic morbidity and mortality [3] and a blunted response to cognitive behavioural therapy for insomnia [4] might be observed. The concomitant objective and subjective assessments might allow the identification of a different subtype of insomnia, nowadays not used in standard classifications of sleep disorders, such as paradoxical insomnia. Efforts exist to achieve an agreed definition of quantitative criteria to identify this subtype of insomnia, which is frequently encountered in clinical practice [5].

The web-based automatic scoring system created by Blanken and colleagues [1] seems to be too complex for use in clinical practice. However, a new subtyping approach based on different methods might add a new page to the history of the insomnia nosology, following the path indicated by the authors with the use of data- driven analysis on large populations. The next challenge will be to establish when an integration with an objective evaluation of the sleep profile should be considered to identify patients with insomnia who are at high-risk for severe medical consequences, and the best therapeutic interventions.

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A.5.2 *Hirakawa H*

I read with interest the Article by Tessa Blanken and colleagues,1 in which the authors identified five novel insomnia disorder subtypes that were differentiated by biologically based traits and life history. In their study, participants with subtype 1 insomnia (highly distressed) showed the highest risk of lifetime depression (88/162 [54·3%]), anxiety (60/162 [37·0%]), and bipolar disorder (8/162 [4·9%]) [1]. Participants with subtype 1 insomnia also showed the highest prevalence of mental and behavioural disorders classified in ICD-10: mood, anxiety, personality, and childhood onset [1]. Half of the participants classified with subtype 1 insomnia reported difficulty initiating sleep by their teenage years [1]. In my opinion, some of the participants diagnosed with depression in subtype 1 insomnia could probably also have been diagnosed with bipolar disorder or bipolar spectrum disorder. Bipolar disorder is characterised by fluctuations in mood state and the onset of symptoms occurs during the teenage years [2]. Sleep disturbance and consequent dysregulation of circadian rhythms have been hypothesised to be a central mechanism in the pathophysiology of bipolar disorder or bipolar spectrum disorder, as well as being a predictor of the first onset and subsequent course of bipolar disorder [3,4].

Therefore, the findings of Blanken and colleagues would be consistent with some of the participants with subtype 1 insomnia having bipolar disorder, but the questionnaires the authors used for classification did not include items that could ascertain this. The authors considered that nearly half of the participants classified with subtype 1 insomnia might have an unknown resilient factor to depression; however, I thought some of the participants had bipolarity and might develop depression intrinsically. I recommend that the authors reanalyse

their data to calculate the percentage of the participants in subtype 1 insomnia who had developed a sleep disturbance by their teenage years and then went on to develop depression or bipolar disorder. By this reanalysis, I anticipate that subtype 1 insomnia could be divided into two additional groups on the basis of the presence of bipolarity.

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B

SUPPLEMENT TO 4: NETWORK OUTCOME ANALYSIS

B.1 SUPPLEMENTARY METHODS AND RESULTS

B.1.1 *Inclusion of sample*

We included participants from the Netherlands Study of Depression and Anxiety (NESDA) [1] who were without a current or prior lifetime Major Depressive Disorder according to the DSM-IV, determined using the Composite International Diagnostic Interview (CIDI) [2], and for whom a CIDI at each of three follow-up measurements was completed. Of the N=2981 participants enrolled in the NESDA, N=1008 were without a current or lifetime diagnosis of depression or dysthymia at baseline. Of these N=1008, N=240 missed at least one of the follow-up measurements T1-T3, resulting in N=768 participants who met our selection criteria. They were between 18 and 65 years of age (M=41.1 years, SD=14.4 years; see supplementary figure B.1 for a histogram), and 482 (62.7%) were female. Most of the included participants (N=526, 68.4%) were free from a current or lifetime diagnosis of any anxiety disorder. Of the remaining 242 participants N=159 (20.7%) had a current diagnosis of any anxiety disorder at baseline, and N=83 (10.8%) had ever been diagnosed with of any anxiety disorder in the past. From the 768 selected participants, the Cox Proportional Hazard analysis included the N=723 participants for whom baseline sleep data were complete. The Network Outcome Analysis (NOA) included the N=743 for whom baseline depression symptoms were complete.

B.1.2 *Network Outcome Analysis*

B.1.2.1 *Network regularization*

LASSO regularization is applied to prevent the inclusion of spurious edges due to sampling variation [3]. The amount of regularization that is applied is controlled by a tuning parameter: a higher tuning parameter omits more edges from the network, resulting in a more sparse network, whereas a lower tuning parameter removes only some edges and a more dense network will be retrieved. The tuning parameter thus controls a trade-off between the in- and exclusion of edges and the number of false positives and false negative edges in the network. The optimal tuning parameter can be selected using either cross-validation or by minimizing the Extended Bayesian Information Criterion (EBIC). When using the EBIC a hyperparameter needs to be set that controls how much the EBIC prefers simpler (i.e., sparser) models, with higher values

corresponding to more sparse networks. Generally, using the EBIC to select the tuning parameter results in sparser networks compared to cross-validation.

For the network estimation reported on in chapter 4, we used the EBIC to select the optimal tuning parameter. The hyperparameter is typically set between 0 and 0.5, where an hyperparameter of 0 errs on the side of discovery and an hyperparameter of 0.5 errs on the side of caution [3]. We adopted the default setting of 0.5 to err on the side of caution. Using this setting NOA identified five symptoms to predict first-onset MDD directly. To evaluate whether some direct effects might have been put to zero by regularisation, we also estimated the networks using a hyperparameter of 0, see supplementary figure B.2. Using this setting in which more edges are estimated, NOA again identified the same five symptoms to be directly predictive of FO-MDD, indicting robustness of our results.

Finally, we estimated the networks using cross-validation to select the tuning parameter, see supplementary figure B.3. As expected, using cross-validation more edges are estimated and a more dense network is retrieved. In addition to the five symptoms that were found using the EBIC, weight change was now also identified as a direct predictor of FO-MDD. Given that this direct link was not found using both hyperparameter settings of the EBIC, and given that cross-validation includes more edges, likely resulting in some spurious edges, it is plausible that this 'direct' predictive effect of weight change on FO-MDD is spurious.

These analyses were performed in R (version 3.5.0) using the packages 'qgraph', 'bootnet', and 'mgm'.

B.1.2.2 *Edge weight accuracy*

After estimating the network edges it is important to assess how accurately these edge-weights are estimated and how robust they are [4]. To evaluate the precision and robustness of the estimated network, the bootnet R-package has been created that uses bootstraps to estimate the accuracy of the network parameters. Specifically, we ran a hundred bootstrap samples for which we fitted the model. For each edge, this results in a hundred estimates of the edge-weight by which we can evaluate how accurate (i.e., what is the range of observed values for a certain parameters?) and how robust (i.e., how often is a parameter larger than zero and thus included into the network?) our original estimate is. It is important to note that because we used LASSO regularization, the edge weights and their sampling distribution are biased towards zero. As a result, plotting the 5% and 95% quantiles might include zero, whereas the corresponding 95% confidence interval does not. Therefore we plot the 5% and 95% quantiles only for the times the parameter was not set to zero. In addition it is shown in how many of the estimated networks the edge weight was put to zero. The resulting sampling distribution for the associations that we have interpreted (i.e., the ones included first-onset MDD) is shown in supplementary figure B.4. For example, the edge weight between 'appetite

change' and 'weight change' was never put to zero (indicated by the 0.0), and its 5% and 95% quantiles lie around 0.15 and 0.35. For a more detailed explanation, see Epskamp, Borsboom, & Fried [5].

B.1.3 *Ancillary analyses*

Network Outcome Analysis (NOA) including age, gender, and presence of any anxiety disorder at baseline did not alter the results, see supplementary figure B.5. In this analysis age was entered as a continuous variable, and sex (male vs. female) and presence of any anxiety disorder at baseline (yes vs. no) as categorical variables. We moreover performed NOA on the subsample of participants (N=609) that were free from any anxiety disorder at baseline. Of these 609 participants, 87 (14.3%) developed a first-onset depression. The results are shown in supplementary figure B.6. As can be seen from both analyses, the relationship between 'difficulty initiating sleep' was robust to either including presence of any anxiety disorder at baseline into the network or excluding the cases with any anxiety disorder at baseline. As can be seen from the table below, the estimated effect was roughly the same across analyses.

Table: Edge weight of the different links between nonclinical baseline depression complaints and first-onset major depressive disorder.

Prospective link	Original analysis	Including anxiety at baseline into the network	Excluding cases with anxiety at baseline
agi – FO-MDD	0.15	0.11	0.00
con – FO-MDD	0.07	0.07	0.05
dep – FO-MDD	0.14	0.14	0.14
dis – FO-MDD	0.08	0.08	0.10
ene – FO-MDD	0.12	0.11	0.11

Abbreviations: agi = psychomotor agitation; con = concentration problems; ene = loss of energy; dis = difficulty initiating sleep; dep = depressed mood.

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B.2 SUPPLEMENTARY FIGURES

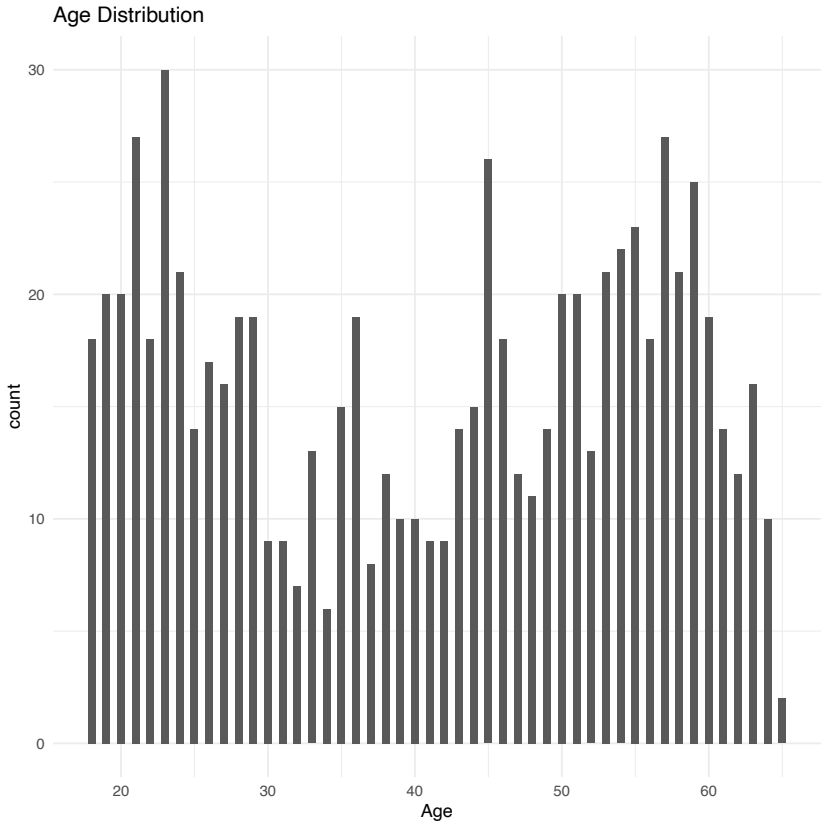

Figure B.1: Age distribution of N=768 participants of the Netherlands Study for Depression and Anxiety that were included in the current study.

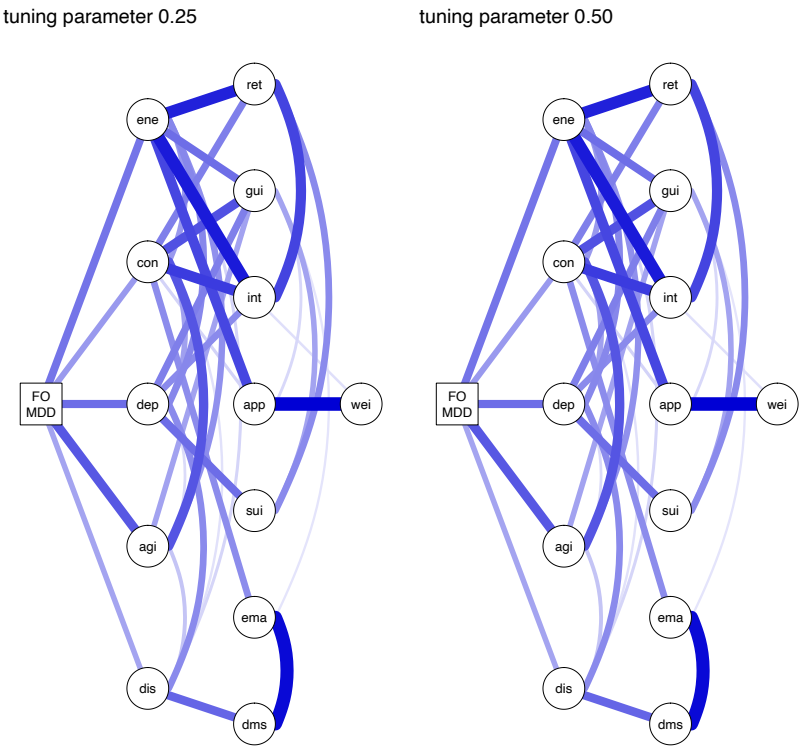

Figure B.2: Estimated regularized networks where the gamma hyperparameter was set to 0.25 (left) or 0.50 (right).

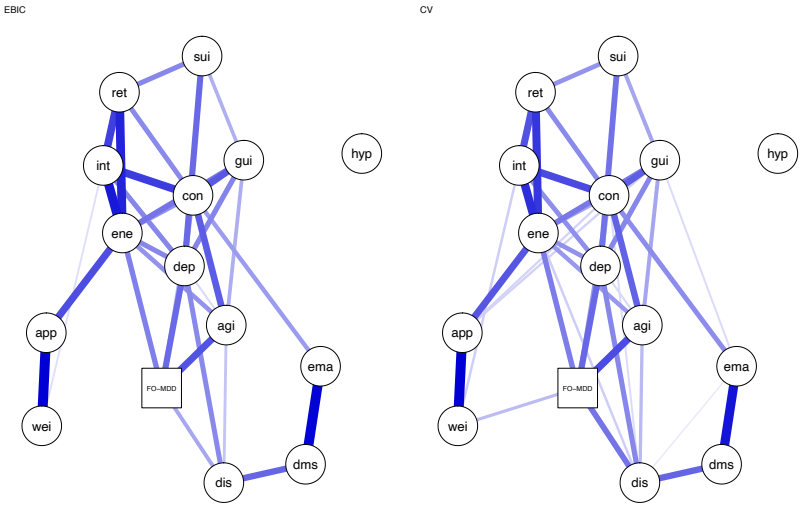

Figure B.3: Estimated regularized networks using EBIC (left) or cross-validation (right) to select the tuning parameter. Note that there is an edge between FO-MDD and 'con' in the EBIC network, that is partially obscured by the edge between FO-MDD and 'dep'. See supplementary information paragraph B.1.2.1 above for details.

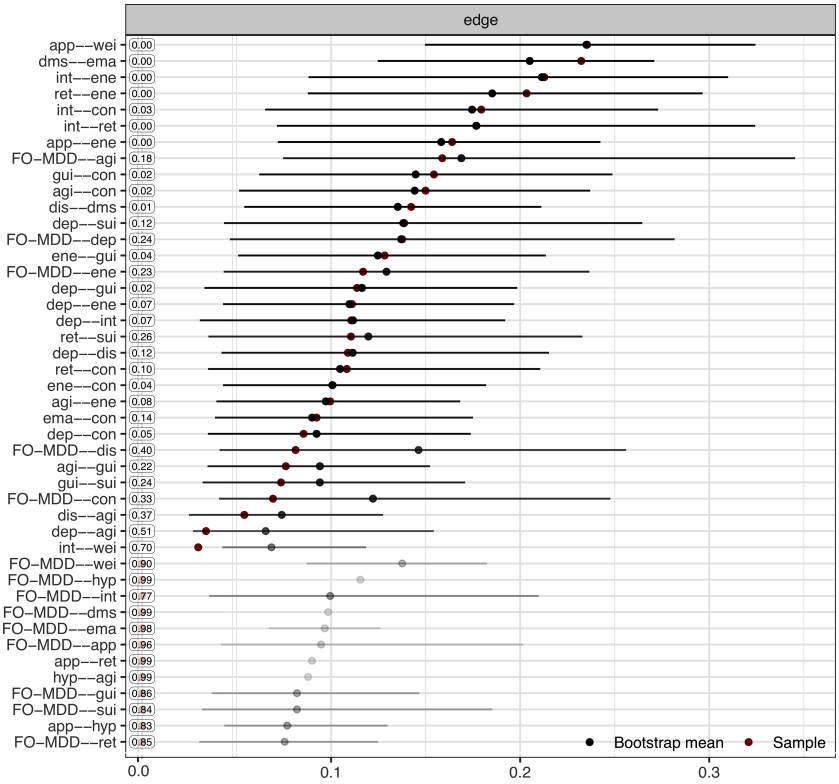

Figure B.4: Bootstrapped sampling distributions zoomed in on the associations that included first-onset MDD. A PDF version containing all bootstrapped associations is available upon request.

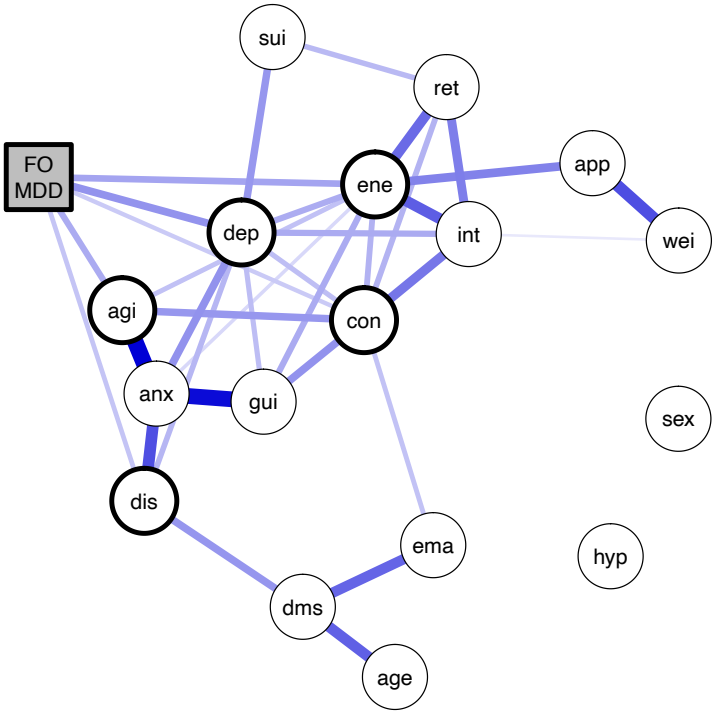

Figure B.5: Network Outcome Analysis including age, sex, and presence of any anxiety disorder (yes vs. no) at baseline. Edges represent conditional dependence relations among the variables and capture unique effects that remain after controlling for all the other variables in the network. The thickness and colour saturation of the edges corresponds to the strength of the association. In this network, all associations are positive. Abbreviations: agi = psychomotor agitation; app = appetite change; con = concentration problems; dep = depressed mood; dis = difficulty initiating sleep; dms = difficulty maintaining sleep; ene = fatigue or loss of energy; ema = early morning awakenings; FO-MDD = first-onset depression; gui = feelings of guilt or worthlessness; hyp = hypersomnia; int = loss of interest; ret = psychomotor retardation; sui = suicidal thoughts; wei = weight change.

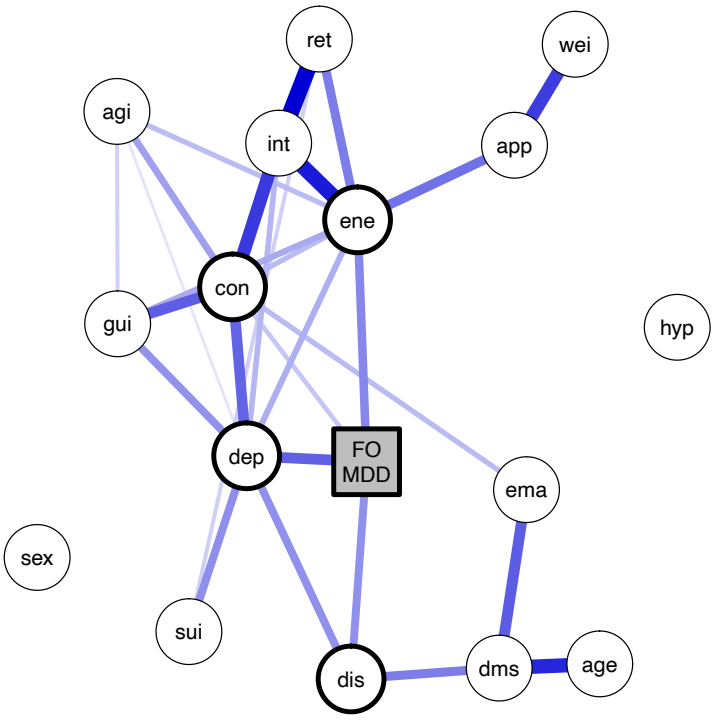

Figure B.6: Network Outcome Analysis on N=609 participants free from any anxiety disorder diagnosis at baseline. Edges represent conditional dependence relations among the variables and capture unique effects that remain after controlling for all the other variables in the network. The thickness and colour saturation of the edges corresponds to the strength of the association. In this network, all associations are positive. Abbreviations: agi = psychomotor agitation; app = appetite change; con = concentration problems; dep = depressed mood; dis = difficulty initiating sleep; dms = difficulty maintaining sleep; ene = fatigue or loss of energy; ema = early morning awakenings; FO-MDD = first-onset depression; gui = feelings of guilt or worthlessness; hyp = hypersomnia; int = loss of interest; ret = psychomotor retardation; sui = suicidal thoughts; wei = weight change.

C

SUPPLEMENT TO 5: NETWORK INTERVENTION ANALYSIS

C.1 SUPPLEMENTARY METHODS AND RESULTS

C.1.1 *Sample characteristics and intervention*

C.1.1.1 *Sample characteristics*

A total of 104 patients (82% female), with a mean±SD age of 45.99 ± 12.32 years, fulfilled self-report DSM-5 criteria of insomnia, and at least subclinical depression (>4 on the PHQ-9). Participants suffered from insomnia for around 10 years (M±SD = 9.79±9.91). At baseline, depression scores ranged from 5-22 (M±SD = 10.19±3.90), from mild (PHQ-9>4) to severe (PHQ-9>19), see also supplementary table C.1. The majority of participants (60%) were highly educated. Participants were recruited online and signed informed consent before randomisation to either CBTI (N=52) or a sleep diary monitoring control group (N=52).

C.1.1.2 *Intervention*

The online CBTI intervention i-Sleep encompasses five modules: (1) sleep hygiene/lifestyle advice, (2) stimulus control and sleep restriction therapy, (3) relaxation techniques, (4) cognitive exercises on dysfunctional thoughts about sleep, and (5) relapse prevention [1]. Participants received online guidance on a weekly basis from a coach (Master students clinical psychology). The study design is shown in supplementary figure C.1. For details, please see Van der Zweerde et al., 2019 [2].

C.1.2 *Network estimation and LASSO regularization*

C.1.2.1 *Network estimation*

For the Network Intervention Analysis (NIA) we selected a Mixed Graphical Model (MGM), implemented in the R-package *mgm* [3], in which we included all symptoms as continuous, and treatment as binary (0: no treatment, 1: treatment). Networks were estimated on the available data for each assessment, resulting in slightly varying sample size (100, 100, 97, 92, 90, 84, 90, 87, 86, 92). In estimating the networks, LASSO regularization was applied to reduce the inclusion of spurious edges, resulting in networks that are easier to interpret and have higher specificity [4]; more details on the regularization in section C.1.2.2). Because the network analyses require the estimation of many parameters, we

performed robustness analyses to assess the accuracy of the estimated edge weights [5], see section C.1.3.

In addition, we estimated the averaged networks for the pre-treatment assessments (T0-T1), for the treatment assessments (T2-T6), and for the post-treatment assessments (T7-T9), see `https://github.com/tfblanken/NIA/tree/master/supplementary_material/averaged`.

C.1.2.2 *LASSO regularization*

The amount of regularization that is applied depends on the LASSO tuning parameter: a low tuning parameter omits only some edges from the network, likely resulting in the inclusion of some spurious edges; a high tuning parameter omits many edges, likely excluding some true edges from the network. Thus, there is a trade-off between the exclusion of edges and the number of false positive and false negative edges in the network – which is controlled by the tuning parameter. The tuning parameter can be selected using either cross-validation or by minimizing the Extended Bayesian Information Criterion (EBIC). For the regularized networks presented in the main text we adopted the default setting of *mgm* and used cross-validation to select the tuning parameter using a gamma hyperparameter of 0.25.

Generally, using the EBIC to select the tuning parameter results in sparser networks compared to cross-validation. We also estimated the networks using EBIC in selecting the tuning parameter. Our results show the same pattern, and sparser networks were estimated when using the EBIC. Importantly, the EBIC did retrieve conditional dependence relations between the binary treatment variable and the sleep problems *difficulty maintaining sleep* and *early morning awakenings*. The networks estimated using EBIC can be accessed online: `https://github.com/tfblanken/NIA/blob/master/supplementary_material`.

We additionally investigated the extent to which the use of LASSO regularization might have altered our interpretations of direct and indirect effects, by putting smaller effects to zero. We did so by estimating all networks using ridge regression. Unlike lasso regularization, ridge regression does not put parameters exactly to zero. Therefore, all estimated direct effects will be present in the network, which allows us to investigate whether there are direct treatment effects that were put to zero by the LASSO regularization. As expected, the ridge regularized networks include more direct treatment effects than are present in the LASSO regularized networks. While this indicates that some direct effects were indeed set to zero, it is important to note that during and after treatment (T2-T9), there are only three symptoms that were directly and negatively associated to the treatment allocation variable in the ridge regularized networks but were not in the LASSO regularized networks: *noticeability of impaired quality of life* (T6), *fatigue* (T8), and *feelings of worthlessness* (T4). During and after treatment, there were other symptoms that were directly and positively related to treatment, indicating favourable treatment "effects" for the control group: *loss of interest* (T2), *difficulty initiating sleep* (T2), *concentration problems* (T3, T4), *noticeability of*

impaired quality of life (T3), *feelings of worthlessness* (T3, T6, T8), and *depressed mood* (T3, T7). Moreover, the ridge regularized networks included treatment "effects" for the pre-treatment assessment weeks, whereas the LASSO regularized network rightfully did not include these effects. The networks estimated using ridge regression can be accessed online: `https://github.com/tfblanken/NIA/blob/master/supplementary_material/NIA_ridge_regression.pdf`.

In sum, the ridge regularized networks include direct treatment "effects" that were put to zero in the LASSO regularized networks. However, these associations more likely reflect slight mean differences between groups rather than actual treatment effects. Given the main objective of NIA to explore possible treatment targets, we would argue that LASSO regularization fits this purpose by selecting the most important edges in the network.

C.1.3 *Edge weight accuracy*

We used the *resample()* function implemented in the *mgm* package to evaluate the edge weight accuracy of the models reported in the main text. For each network model, we ran a hundred bootstrap samples for which we fitted the model. We subsequently plotted the resulting sampling distribution of all edges using the function *plotRes()*, also implemented in the *mgm* package. The plot shows the 5% and 95% quantiles of the sampling distribution and the proportion of estimates whose absolute values were larger than zero. Notably, because we used LASSO regularization in estimating the networks, the edge weights and their sampling distribution are biased towards zero. As a result, the 5% and 95% quantiles might include zero, whereas the corresponding 95% confidence interval does not. If the 5% and 95% quantiles do not contain zero, this ascertains that the 95% confidence interval does not either. For a more detailed explanation, see Epskamp, Borsboom, & Fried (2017) [5]. The resulting sampling distributions are shown in supplementary figure 2. For example, in the estimated network of week 1, the edge weight between *depressed mood* and *feelings of worthlessness* was larger than zero in 100% of the bootstrap samples, and its 5% and 95% quantiles lie around 0.30 and 0.60.

C.1.4 *Visualizing effect on symptom severity in node sizes*

To visualize the differences in symptom severity between treatment and control condition, we first standardized the item-means for each assessment to the pooled baseline mean and standard deviation. After standardization, negative values indicate a decrease in symptom severity compared to baseline level, while positive values indicate an increase in symptom severity compared to baseline level. We computed the standardized item-means for the treatment and control group separately. Comparing the standardized item-means of the treatment group to the control group gives us an indication of the effect of CBTI on the severity of specific symptoms. Any reduction in symptom severity in

the treatment group *over and above* the reduction in symptom severity in the control group is likely due to the CBTI treatment. Specifically, we visualized the improvement in symptom severity in the treatment group *compared with* the improvement in symptom severity in the control group. For example, on the post-assessment, the average *difficulty initiating sleep* was M=1.60 in the control group and M=1.11 in the treatment group, respectively. Standardized to the overall M±SD of 2.25±1.53 on difficulty initiating sleep during baseline, there is a reduction of -0.43 and -0.75, respectively. Thus, the treatment group improved -0.32 more than the control group, which is visualized in a smaller node size representing reduced symptom severity. Because we have accounted for the improvement in the control group, this improvement can be interpreted as induced by CBTI treatment. The raw item means are given in supplementary table C.2 and the standardized scores and differences can be found in supplementary table C.3.

C.1.5 *Exploring the relation between predictability and variance of the symptoms*

The predictability (i.e., proportion of explained variance) of the symptoms [6] increased over the course of treatment, see supplementary table C.4. We explored whether this increase might be explained by increased or decreased variability in the symptom scores over the course of treatment. To investigate this possibility, we first computed the observed variance in the symptoms for each week and evaluated its changes over time. The variance did not systematically increase or decrease over time. For example, compared to baseline, the variance at post-assessment increased for 8 symptoms (maximum increase of 0.50) and decreased for 7 symptoms (maximum decrease of 0.31), with an average difference of 0.04. Second, for each variable, we correlated the variance at each assessment to the observed predictability, which was, on average, only r=0.14 (range: -0.58 to 0.93). This correlation was significant for only three variables ('worry about sleep', 'loss of interest', and 'suicidal thoughts'; of which only the first two survived Bonferroni corrections). Thus, while the predictability consistently increased for all symptoms but two ('feelings of worthlessness' and 'depressed mood'), the observed variance did not show such a systematic pattern. Because the range of the correlation between the variance and predictability is quite large for some symptoms, we finally investigated whether this absolute correlation was related to the amount of increase in predictability. If this would be the case, then this would indicate that there might be a relationship between variance and predictability, but only for those variables that show the largest increase. The small correlation of r=0.14 ($t(13)=0.53$, $p=0.60$) indicated that this was not the case. Taken together, these results indicate that the increase in predictability does not simply reflect an increase or decrease in variance.

C.1.6 *Baseline differences*

There were no baseline differences in symptom severity between the treatment groups (all p>0.26) except for 'loss of interest' (t(98.3)=2.31, p=0.02; non-significant after Bonferroni corrections). It is important to note that for the current study the participants were randomly allocated to either the treatment or control condition. Group membership was thus not based on baseline severity. Nonetheless, to ensure that the treatment effect was not confounded by baseline differences between groups, we repeated the analyses excluding the symptom 'loss of interest', that differed between groups at baseline. The results can be find here: `https://github.com/tfblanken/NIA/blob/master/supplementary_material/NIA_excluding_Loss_Of_Interest.pdf`. Importantly, none of the estimated treatment effects changed when omitting 'loss of interest' from the network estimations. In sum, because of randomization the two groups did not differ in baseline symptom severity, except for one symptom, but this difference did not affect the estimated treatment effects.

C.1.7 *Exploring the effect of baseline symptom severity on the estimated treatment effects*

Symptoms that are higher in severity at baseline have a higher probability to go down during treatment. In previous research (e.g., [7]) it was seen that the treatment effects were larger for symptoms with higher baseline severity. We investigated whether baseline symptom severity explained the differential effects of cognitive behavioural therapy for insomnia (CBTI) on the insomnia symptoms. First, we correlated the average baseline insomnia symptom severity to the treatment effect (time*condition Cohen's d effect sizes, given in supplementary table C.5), which was non-significant, r=0.63, t(5)=1.81, p=0.13. Second, we investigated, for each participant, which of the insomnia symptoms was reported to be most severe at baseline. We listed all symptoms that were indicated to be most severe, in case the highest severity score was given to multiple symptoms. For each of the insomnia symptoms, we then computed the proportion of participants for which this symptom was worst at baseline, shown in the figure below. The rank-order of these proportions was not associated to the rank-order of the Cohen's d effect sizes (ρ=-0.14, S=64, p=0.78). Both results indicated that, although the symptom severity affects the probability of the symptom severity to go down during treatment, it seems unlikely that this explains the differential effect of treatment on the symptoms.

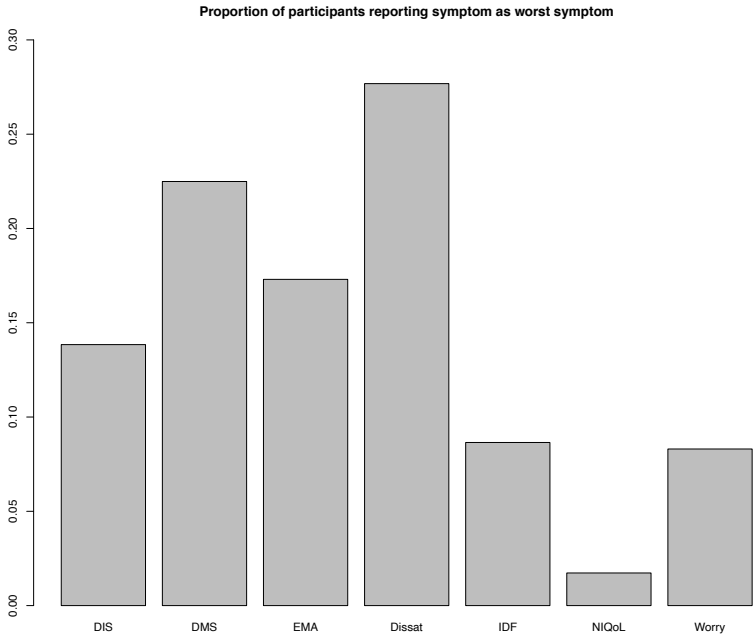

Figure: Proportion of participants that indicated a specific symptom to be most severe at baseline. For each participant, we listed the symptom(s) that were indicated to be most severe at baseline. For each symptom, we then computed the proportion of participants that listed this symptom as most severe, which is shown in this figure. The time*condition Cohen's *d* effect sizes of the symptoms were: 0.38, 1.59, 1.37, 1.28, 0.92, 0.84, 1.46, respectively. The rank-order correlation between the proportion of participant listing a symptom as most severe and the Cohen's *d* effect size was ρ=0.14 (S=64, ρ=0.78).

C.1.8 *Reproducibility*

For reproducibility, the adjacency matrices of the regularized networks can be shared upon request. The R-scripts can be accessed through `https://github.com/tfblanken/NIA/tree/master/R-scripts`.

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C.2 SUPPLEMENTARY TABLES

Table C.1: Baseline and post-assessment M(±SD) in treatment and control gorup.

		N	Baseline M(±SD)	N	Post-assessment M(±SD)
PHQ-9	T	52	10.1 (4.19)	45	4.20 (3.57)
	C	52	9.54 (3.53)	47	7.89 (4.67)
PHQ-WS	T	52	7.58 (3.99)	45	3.07 (3.09)
	C	52	7.10 (3.44)	47	5.74 (4.22)
ISI	T	52	19.16 (3.76)	45	9.24 (5.41)
	C	52	18.83 (3.19)	47	17.09 (5.17)

Note. C = Control, sleep monitoring no treatment condition; T = Treatment; i-Sleep online CBT-I condition; ISI = Insomnia Severity Index; PHQ-9 = Patient Health Questionnaire-9; PHQ-WS = Patient Health Questionnaire minus Sleep item.

Table C.2: Item means for each week, for the control condition (upper panel) and treatment condition (lower panel) separately.

		Insomnia Severity Index items							Patient Health Questionnaire items							
	Week	DIS	DMS	EMA	Dissat	IDF	NIQoL	Worry	LoI	Dep Mood	Fatigue	Appet	Worth	Con	Psych Mot	Sui
Control condition	T0	2.15	3.13	2.75	3.54	2.83	1.73	2.69	0.75	0.60	1.98	0.94	0.88	1.38	0.46	0.10
	T1	1.23	2.12	2.04	2.40	1.71	1.29	1.50	0.77	0.52	1.94	0.98	0.46	1.17	0.29	0.12
	T2	1.60	3.00	2.66	3.17	2.60	1.74	2.57	0.70	0.49	1.70	0.77	0.55	1.13	0.30	0.11
	T3	1.56	2.89	2.58	3.27	2.49	1.47	2.53	0.91	0.56	1.56	0.78	0.42	1.11	0.22	0.13
	T4	1.45	2.86	2.39	3.14	2.52	1.64	2.66	0.73	0.57	1.57	0.77	0.48	1.16	0.32	0.11
	T5	1.07	2.68	2.34	3.10	2.41	1.59	2.46	0.78	0.59	1.68	0.76	0.44	1.07	0.15	0.20
	T6	1.35	2.93	2.40	3.14	2.35	1.70	2.44	0.70	0.58	1.44	0.74	0.35	0.93	0.19	0.14
	T7	1.48	2.80	2.50	3.05	2.32	1.50	2.55	0.70	0.45	1.39	0.68	0.32	0.93	0.27	0.20
	T8	1.40	2.91	2.44	3.00	2.47	1.79	2.51	0.79	0.63	1.67	0.79	0.40	1.09	0.23	0.14
	T9	1.60	2.94	2.70	3.19	2.36	1.64	2.66	0.79	0.55	1.51	0.79	0.49	1.17	0.30	0.15
Treatment condition	T0	2.35	3.13	2.65	3.52	2.81	1.92	2.73	1.13	0.77	2.10	1.10	0.75	1.23	0.38	0.12
	T1	1.50	2.46	1.67	2.56	1.52	1.40	1.62	0.87	0.63	2.04	1.06	0.67	1.17	0.37	0.02
	T2 (T)	1.96	2.60	1.94	3.04	2.56	1.76	2.48	0.84	0.54	1.56	0.94	0.58	0.96	0.24	0.06
	T3 (T)	1.64	2.21	2.02	3.02	2.49	1.74	2.43	0.91	0.72	1.57	0.91	0.55	1.34	0.34	0.09
	T4 (T)	1.39	1.89	1.41	2.61	2.26	1.52	2.09	0.70	0.43	1.61	0.83	0.28	1.09	0.17	0.02
	T5 (T)	1.14	1.63	1.37	2.44	1.95	1.33	1.91	0.60	0.40	1.42	0.74	0.35	0.95	0.14	0.02
	T6 (T)	1.13	1.38	1.36	2.23	1.77	1.09	1.51	0.51	0.36	1.17	0.60	0.28	0.70	0.11	0.02
	T7	1.00	1.33	1.12	1.95	1.49	1.00	1.40	0.49	0.44	0.93	0.42	0.26	0.72	0.07	0.00
	T8	1.05	1.40	1.21	1.93	1.44	1.02	1.42	0.47	0.40	0.95	0.44	0.21	0.65	0.07	0.00
	T9	1.11	1.27	1.16	1.98	1.44	1.00	1.29	0.44	0.40	0.89	0.47	0.20	0.58	0.07	0.02

Note. DIS = difficulty initiating sleep; DMS = difficulty maintaining sleep; EMA = early morning awakenings; Dissat = dissatisfaction functioning; NIQoL = noticability of impaired quality of life; Worry = worry about sleep; LoI = loss of interest; Dep Mood = depressed mood; Appet = appetite change; Worth of worthlessness; Con = concentration problems; Psych Mot = psychomotor agitation; Sui = suicidal thoughts.

Table C.3: Item means, standardized to overall mean and standard deviation at baseline (To). Differences indicate the standardized improvement of treatment condition over and above the improvement in the control condition.

		Insomnia Severity Index items							Patient Health Questionnaire items							
		DIS	DMS	EMA	Dissat	IDF	NIQoL	Worry	LoI	Dep Mood	Fatigue	Appet	Worth	Con	Psych Mot	Sui
Overall baseline (*M*±*SD*)		2.25 ± 1.52	3.13 ± 1.05	2.70 ± 1.37	3.53 ± 0.54	2.82 ± 0.68	1.83 ± 0.88	2.71 ± 0.86	0.94 ± 0.87	0.68 ± 0.79	2.04 ± 0.87	1.02 ± 0.94	0.82 ± 0.96	1.31 ± 0.98	0.42 ± 0.73	0.11 ± 0.31
T1	Control[a]	-0.67	-0.96	-0.48	-2.10	-1.63	-0.61	-1.42	-0.20	-0.20	-0.12	-0.04	-0.37	-0.14	-0.18	0.06
	Treatment[a]	-0.49	-0.64	-0.75	-1.80	-1.91	-0.48	-1.28	-0.09	-0.06	0.00	0.04	-0.15	-0.14	-0.08	-0.28
	Difference	0.18	0.32	-0.27	0.30	-0.28	0.13	0.13	0.11	0.14	0.12	0.08	0.22	0.01	0.10	-0.34
T2	Control[a]	-0.43	-0.13	-0.03	-0.67	-0.33	-0.09	-0.16	-0.28	-0.24	-0.39	-0.27	-0.27	-0.18	-0.17	0.00
	Treatment[a]	-0.49	-0.64	-0.75	-1.80	-1.91	-0.48	-1.28	-0.09	-0.06	0.00	0.04	-0.15	-0.14	-0.08	-0.28
	Difference	0.24	-0.38	-0.52	-0.24	-0.05	0.02	-0.11	0.16	0.06	-0.16	0.18	0.03	-0.17	-0.08	-0.15
T3	Control[a]	-0.46	-0.23	-0.09	-0.49	-0.48	-0.41	-0.21	-0.04	-0.16	-0.56	-0.26	-0.41	-0.20	-0.27	0.09
	Treatment[a]	-0.40	-0.88	-0.50	-0.94	-0.48	-0.09	-0.33	-0.03	0.05	-0.53	-0.11	-0.27	0.03	-0.11	-0.07
	Difference	0.05	-0.64	-0.41	-0.46	0.00	0.32	-0.13	0.00	0.21	0.02	0.15	0.14	0.23	0.16	-0.16
T4	Control[a]	-0.52	-0.26	-0.23	-0.73	-0.43	-0.22	-0.06	-0.25	-0.14	-0.54	-0.26	-0.35	-0.15	-0.14	0.03
	Treatment[a]	-0.56	-1.18	-0.94	-1.71	-0.82	-0.35	-0.73	-0.28	-0.31	-0.49	-0.2	-0.56	-0.23	-0.34	-0.27
	Difference	-0.04	-0.92	-0.71	-0.98	-0.39	-0.13	-0.67	-0.04	-0.17	0.05	0.06	-0.20	-0.07	-0.20	-0.30
T5	Control[a]	-0.77	-0.43	-0.26	-0.80	-0.59	-0.28	-0.29	-0.19	-0.12	-0.41	-0.28	-0.39	-0.24	-0.38	0.29
	Treatment[a]	-0.73	-1.43	-0.97	-2.02	-1.27	-0.57	-0.94	-0.39	-0.36	-0.71	-0.29	-0.49	-0.36	-0.39	-0.27
	Difference	0.04	-1.00	-0.71	-1.22	-0.68	-0.30	-0.65	-0.20	-0.24	-0.3	-0.01	-0.09	-0.12	-0.01	-0.56
T6	Control[a]	-0.59	-0.19	-0.22	-0.72	-0.69	-0.15	-0.32	-0.28	-0.13	-0.69	-0.29	-0.49	-0.39	-0.32	0.11
	Treatment[a]	-0.74	-1.66	-0.98	-2.40	-1.55	-0.85	-1.40	-0.50	-0.41	-1.00	-0.45	-0.56	-0.62	-0.43	-0.27
	Difference	-0.15	-1.47	-0.75	-1.68	-0.86	-0.70	-1.09	-0.22	-0.28	-0.31	-0.16	-0.08	-0.23	-0.11	-0.38
T7	Control[a]	-0.51	-0.32	-0.15	-0.90	-0.73	-0.37	-0.19	-0.27	-0.29	-0.75	-0.36	-0.52	-0.39	-0.21	0.32
	Treatment[a]	-0.82	-1.72	-1.16	-2.92	-1.96	-0.94	-1.54	-0.52	-0.30	-1.27	-0.64	-0.58	-0.60	-0.48	-0.34
	Difference	-0.31	-1.4	-1.01	-2.03	-1.22	-0.57	-1.34	-0.25	-0.02	-0.52	-0.28	-0.06	-0.22	-0.28	-0.66
T8	Control[a]	-0.56	-0.22	-0.19	-0.98	-0.52	-0.04	-0.23	-0.17	-0.07	-0.42	-0.24	-0.44	-0.22	-0.26	0.11
	Treatment[a]	-0.79	-1.65	-1.09	-2.97	-2.02	-0.92	-1.51	-0.55	-0.36	-1.25	-0.61	-0.63	-0.67	-0.48	-0.34
	Difference	-0.23	-1.44	-0.90	-1.99	-1.51	-0.88	-1.28	-0.37	-0.29	-0.83	-0.37	-0.19	-0.45	-0.22	-0.45
T9	Control[a]	-0.43	-0.19	0.00	-0.63	-0.67	-0.22	-0.06	-0.18	-0.16	-0.61	-0.25	-0.34	-0.14	-0.17	0.14
	Treatment[a]	-0.75	-1.77	-1.13	-2.88	-2.02	-0.94	-1.66	-0.57	-0.36	-1.32	-0.58	-0.64	-0.75	-0.49	-0.27
	Difference	-0.32	-1.59	-1.13	-2.25	-1.35	-0.73	-1.60	-0.39	-0.19	-0.72	-0.34	-0.30	-0.61	-0.32	-0.41

[a] Item mean standardized to baseline mean and standard deviation.

Note. DIS = difficulty initiating sleep; DMS = difficulty maintaining sleep; EMA = early morning awakenings; Dissat = dissatisfaction functioning; NIQoL = noticability of impaired quality of life; Worry = worry about sleep; LoI = loss of interest; Dep Mood = depressed mood; Appet = appetite change; Worth of worthlessness; Con = concentration problems; Psych Mot = psychomotor agitation; Sui = suicidal thoughts.

Table C.4: Mean predictability.

	T0	T1	T2(T)	T3(T)	T4(T)	T5(T)	T6(T)	T7	T8	T9
Mean overall predictability	30%	20%	37%	45%	43%	46%	55%	58%	51%	53%
Mean predictability insomnia symptoms	29%	11%	38%	40%	47%	48%	58%	61%	60%	62%
Mean predictability depression symptoms	31%	27%	36%	48%	39%	45%	53%	55%	43%	46%

Note. We computed the mean predictability at each assessment and explored changes over time. Surprisingly, treatment seems to systematically and robustly increase predictability over time: from, on average, 30% explained variance at baseline to, on average, 53% at post-assessment. One explanation for the increase in predictability might be the direct associations that the treatment allocation variable has in the regularized network. To explore the effect of these direct effects on predictability, we re-estimated the networks without the treatment allocation variable. Even without the treatment allocation variable, the predictability increased over time from 31% at baseline to 53% at post-assessment. This indicates that the increase in predictability reflects something other than the direct associations of the treatment allocation variable. Possibly, treatment changes the regularized network structure of the symptoms, which would then be reflected in an increased predictability. In line with this possibility, it is important to note that the increase in predictability is especially pronounced in the insomnia symptoms – for which the treatment effect was largest: from, 29% at baseline to 62% at post-assessment; compared to an increase of the depression symptoms from 31% at baseline to 46% at post-assessment. We explored whether this increase might be associated to an in- or decrease in variability of the symptoms over time, but this was not the case (see Supplementary Methods and Results 4). However, alternative explanations like methodological artefacts as the result of repeated assessments should be explored.

Table C.5: Effect sizes Time × Condition (Cohen's d^a) per item of Insomnia Severity Index and Patient Health Questionnaire pre-assessment vs. week 1-9.

	Insomnia Severity Index							Patient Health Questionnaire								
	DIS	DMS	EMA	Dissat	IDF	NIQol	Worry	LoI	Dep Mood	Sleep[b]	Fatigue	Appet	Worth	Con	Psych Mot	Sui
T1	0.00	0.24	0.28	0.14	0.16	0.00	0.06	0.41	0.13	0.17	0.06	0.16	0.31	0.13	0.23	0.35
T2	0.16	0.39	0.64	0.17	0.00	0.11	0.18	0.29	0.14	0.36	0.29	0.00	0.17	0.00	0.14	0.17
T3	0.11	0.53	0.38	0.35	0.06	0.14	0.22	0.44	0.06	0.65	0.06	0.00	0.17	0.51	0.40	0.21
T4	0.37	0.97	0.90	0.64	0.18	0.19	0.77	0.45	0.33	0.77	0.06	0.00	0.00	0.22	0.09	0.21
T5	0.14	0.75	0.76	0.85	0.39	0.35	0.69	0.61	0.39	0.99	0.20	0.00	0.00	0.06	0.23	0.38
T6	0.34	1.52	0.85	1.03	0.40	0.75	1.15	0.60	0.45	1.01	0.29	0.23	0.00	0.11	0.00	0.31
T7	0.45	1.42	1.18	1.04	0.81	0.57	1.24	0.56	0.11	0.97	0.43	0.21	0.22	0.06	0.06	0.51
T8	0.40	1.32	0.98	1.11	0.97	0.84	1.35	0.60	0.38	1.11	0.69	0.42	0.06	0.26	0.06	0.37
T9	0.38	1.59	1.37	1.28	0.92	0.84	1.46	0.78	0.29	1.11	0.67	0.40	0.13	0.54	0.17	0.41

[a] Cohen's d converted from partial η^2 using formula from Cohen (1988). Partial η^2 were obtained from the SPSS analysis and then recalculated into Cohen's d's for interpretability as the distance between the two means expressed in standard deviations: $f^2 = \frac{\eta^2}{(1-\eta^2)}$, f^2 being the square of the effect size, and therefore $f = \sqrt{\frac{\eta^2}{(1-\eta^2)}}$ and $d = 2 \times f$.

[b] Sleep item taken out of the effect analysis (PHQ-WS). DIS = difficulty initiating sleep; DMS = difficulty maintaining sleep; EMA = early morning awakenings; Dissat = dissatisfaction functioning; NIQoL = noticability of impaired quality of life; Worry = worry about sleep; LoI = loss of interest; Dep Mood = depressed mood; Appet = appetite change; Worth of worthlessness; Con = concentration problems; Psych Mot = psychomotor agitation; Sui = suicidal thoughts. Cohen's d is considered small (< 0.20), moderate (around 0.50) or large (≥ 0.80; Cohen, 1988)

C.3 SUPPLEMENTARY FIGURES

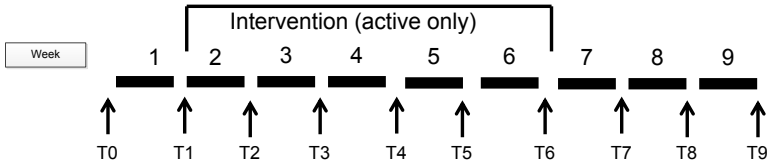
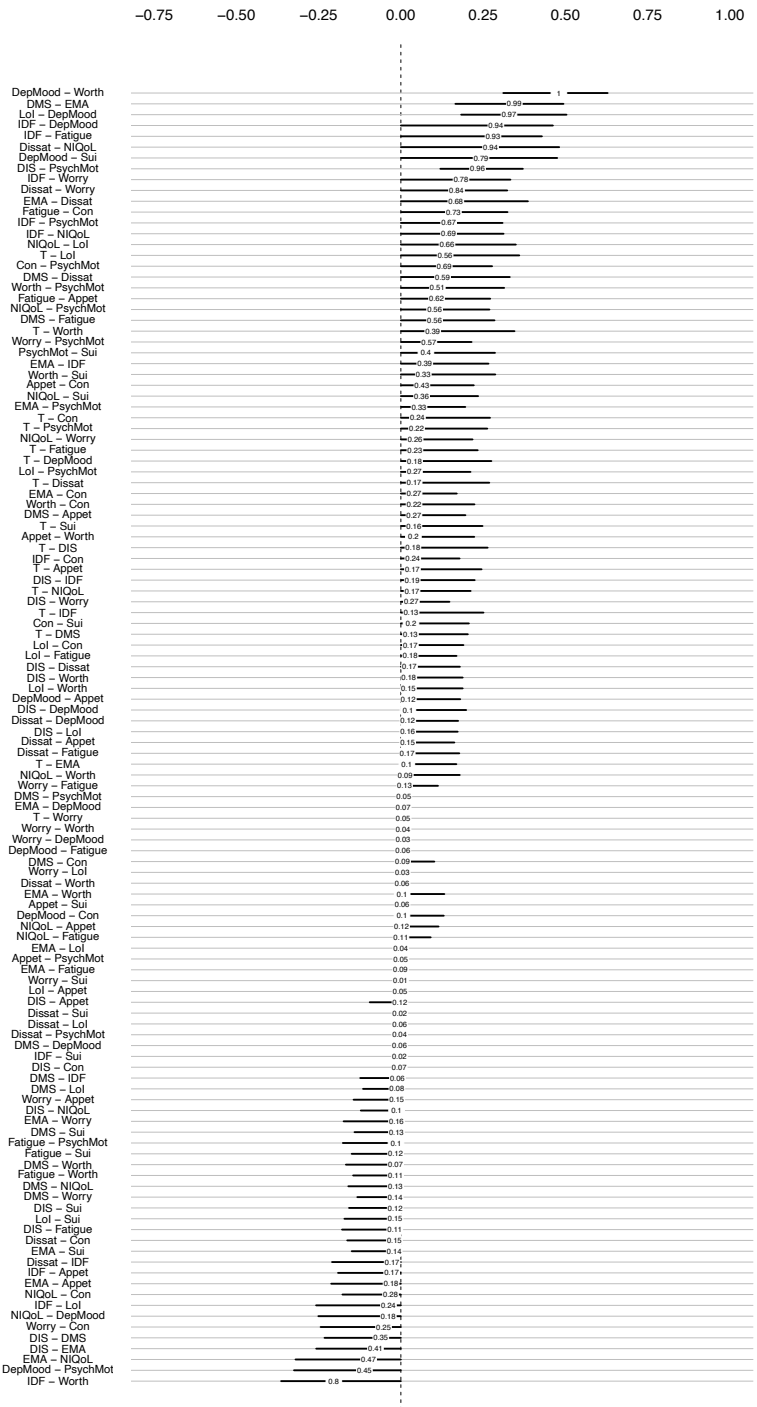
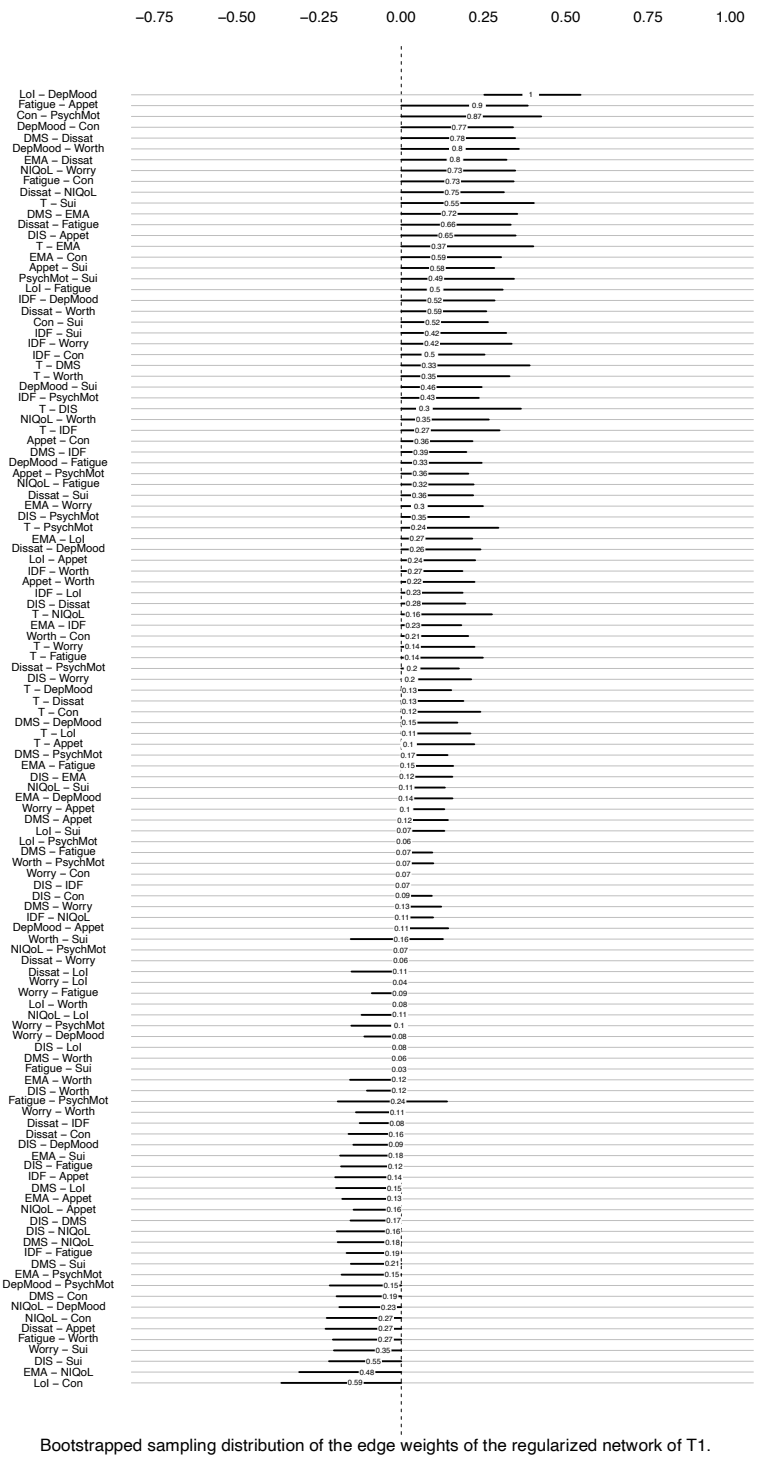


Figure C.1: Study design. Data were collected in a randomised controlled trial on effects of online CBTI on insomnia and depression symptoms (Van der Zweerde et al., 2018). Participants (N=104) were asked to complete an online sleep diary daily and the Patient Health Questionnaire-9 (PHQ-9; Spitzer, Kroenke & Williams, 1999) and Insomnia Severity Index (ISI; Bastien, Vallieres & Morin, 2001) every week, for 10 weeks. Participants allocated to the CBTI condition received online treatment I- Sleep for five weeks. Nine weeks after randomisation the last post-assessment took place. Participants in the control condition were then offered the intervention. Most participants (N=41, 85%) completed the entire i-Sleep intervention, 7 participants completed one (N=3), two (N=1), or four sessions (N=3), 4 did not start. Further details and treatment effects are reported elsewhere (Van der Zweerde et al., 2018).

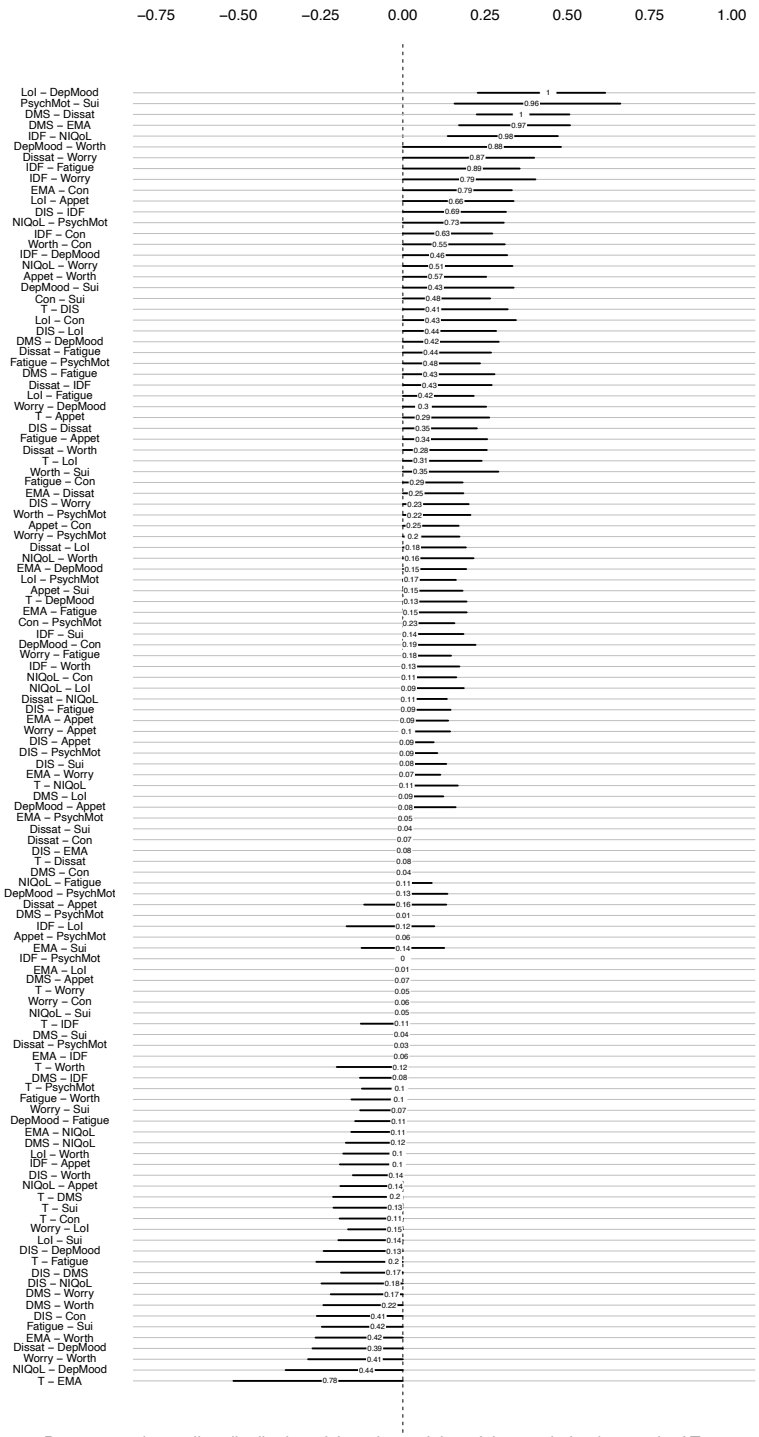
Figure 2.



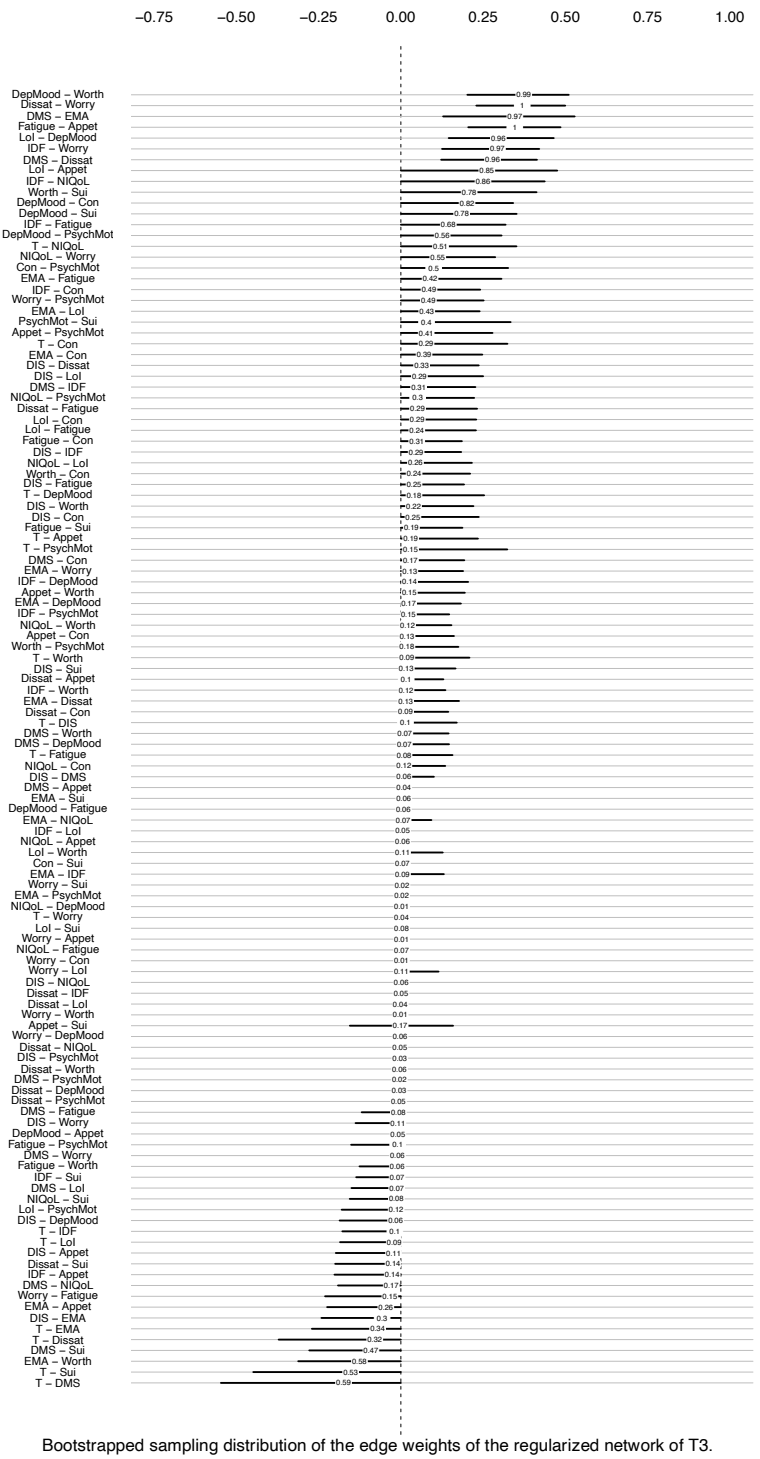
Bootstrapped sampling distribution of the edge weights of the regularized network of T0.



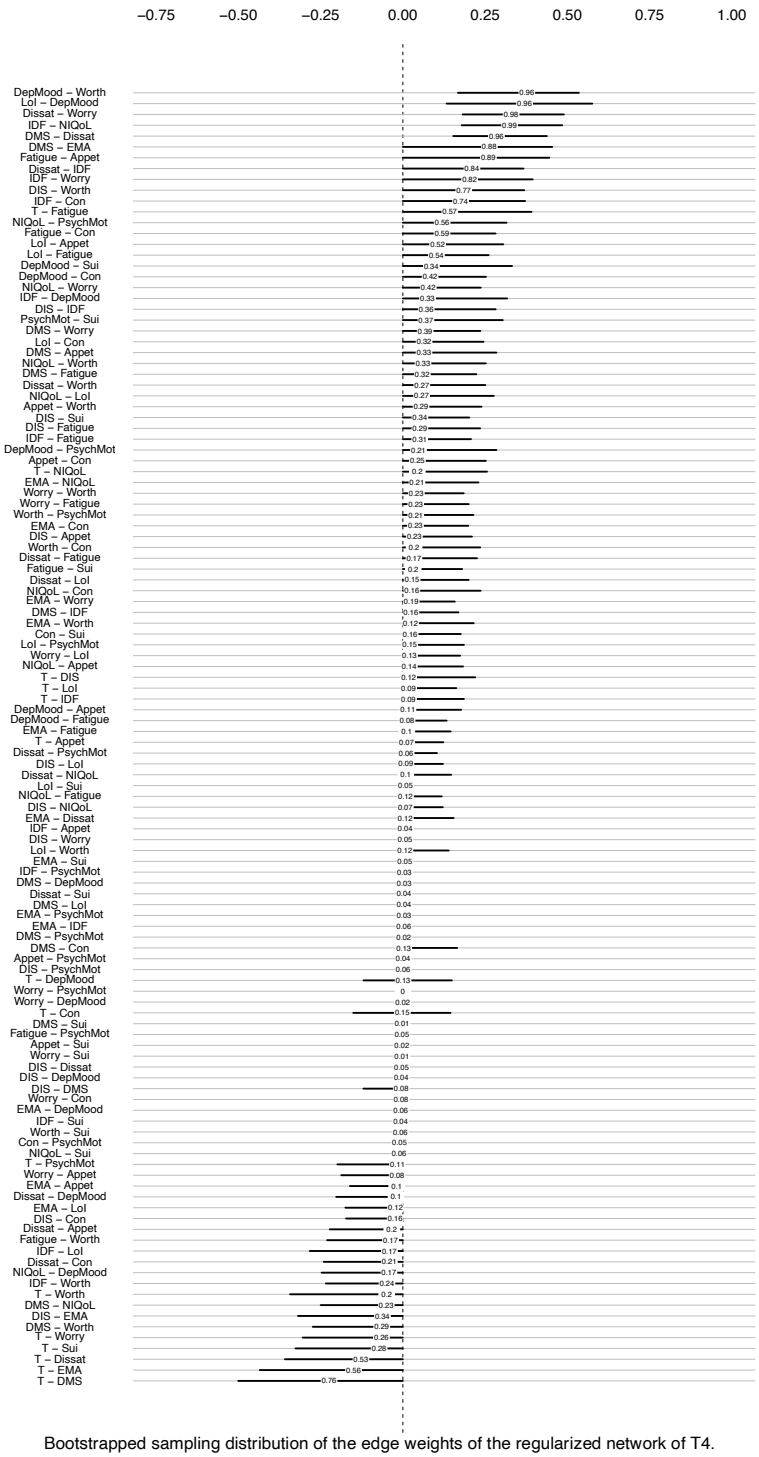
Bootstrapped sampling distribution of the edge weights of the regularized network of T1.



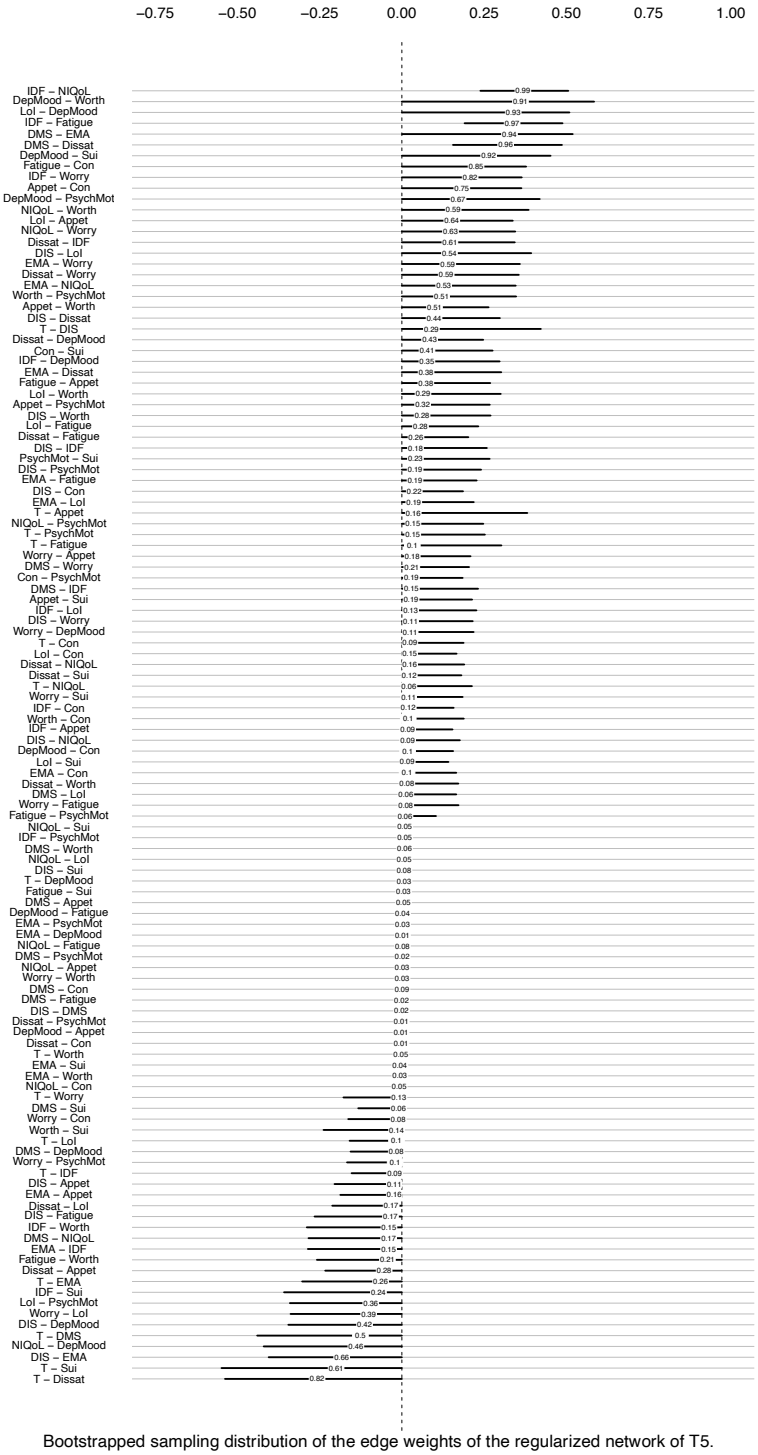
Bootstrapped sampling distribution of the edge weights of the regularized network of T2.



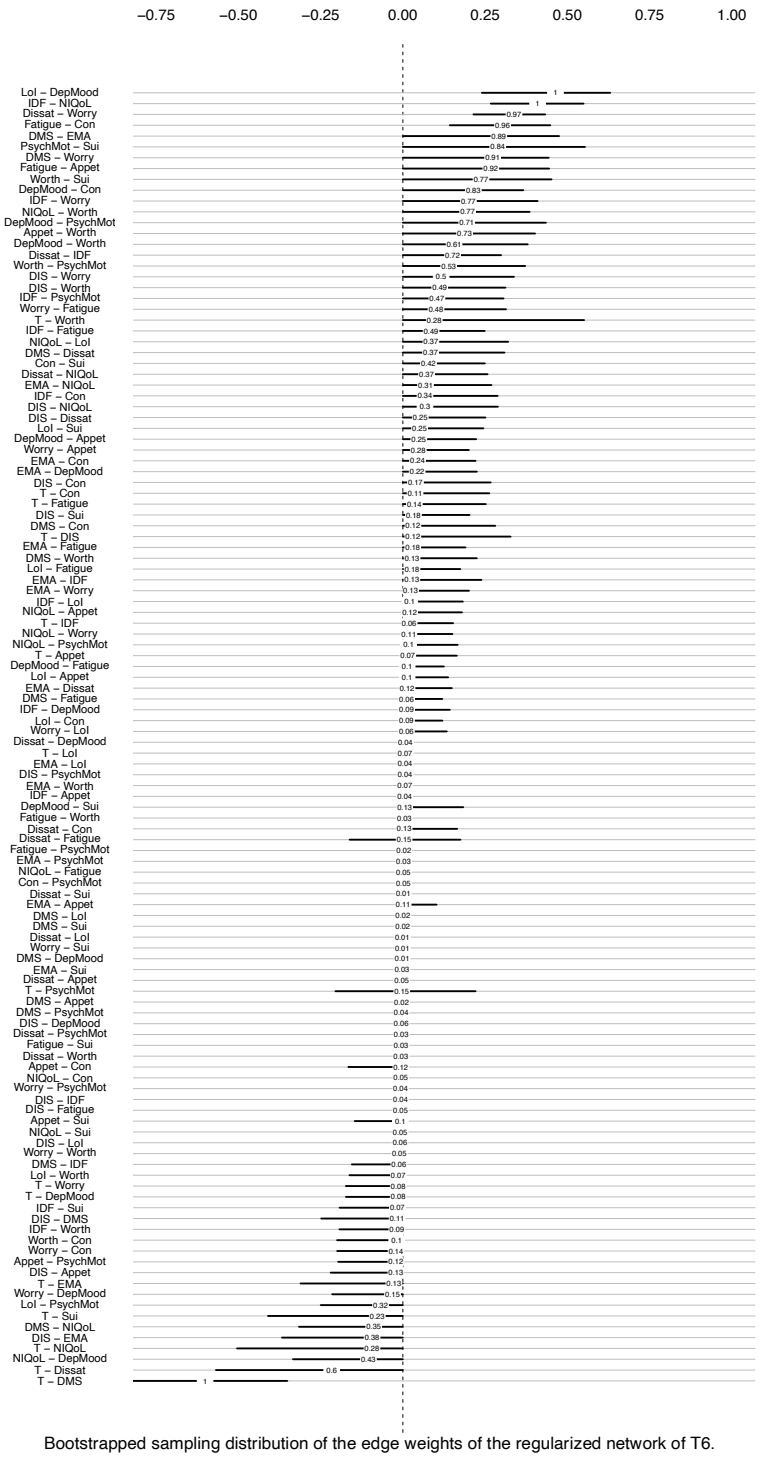
Bootstrapped sampling distribution of the edge weights of the regularized network of T3.



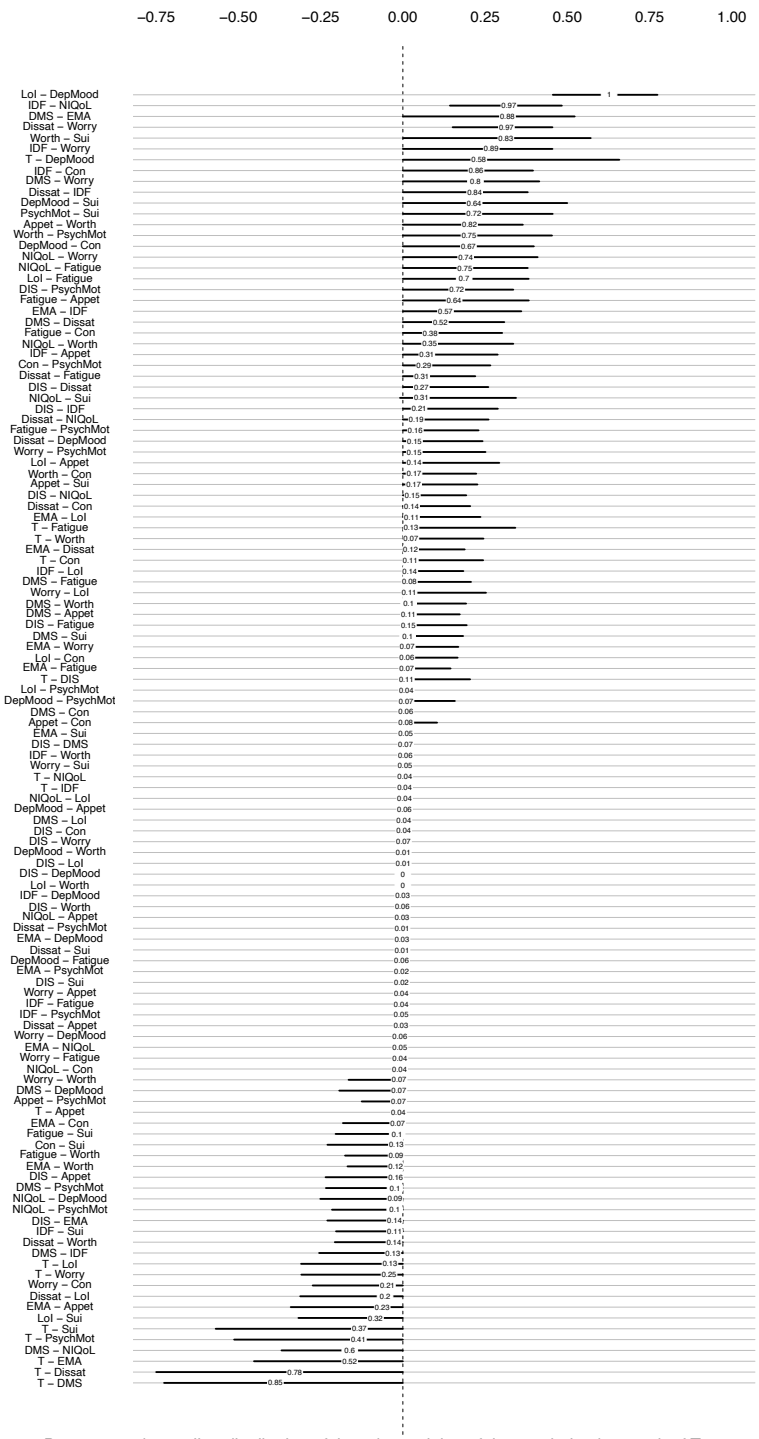
Bootstrapped sampling distribution of the edge weights of the regularized network of T4.



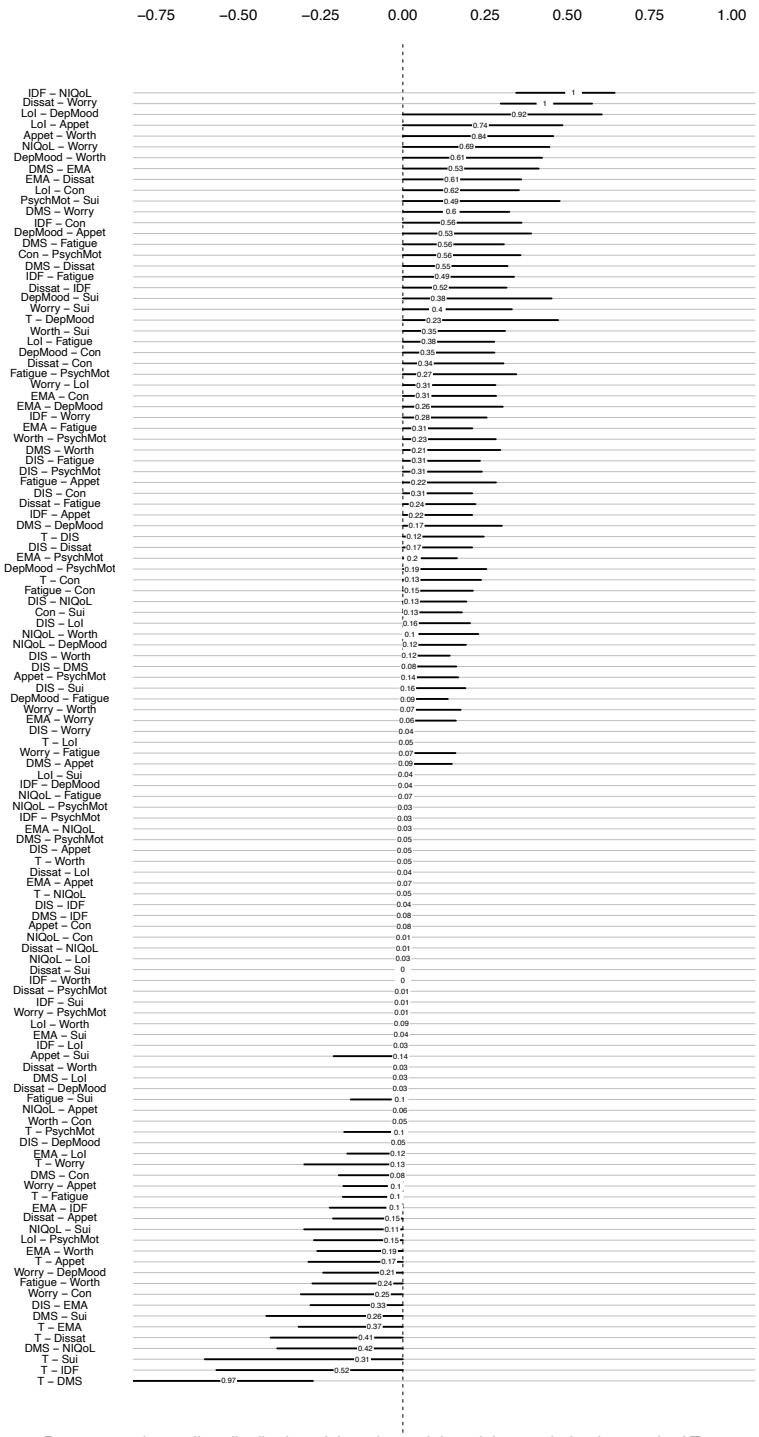
Bootstrapped sampling distribution of the edge weights of the regularized network of T5.



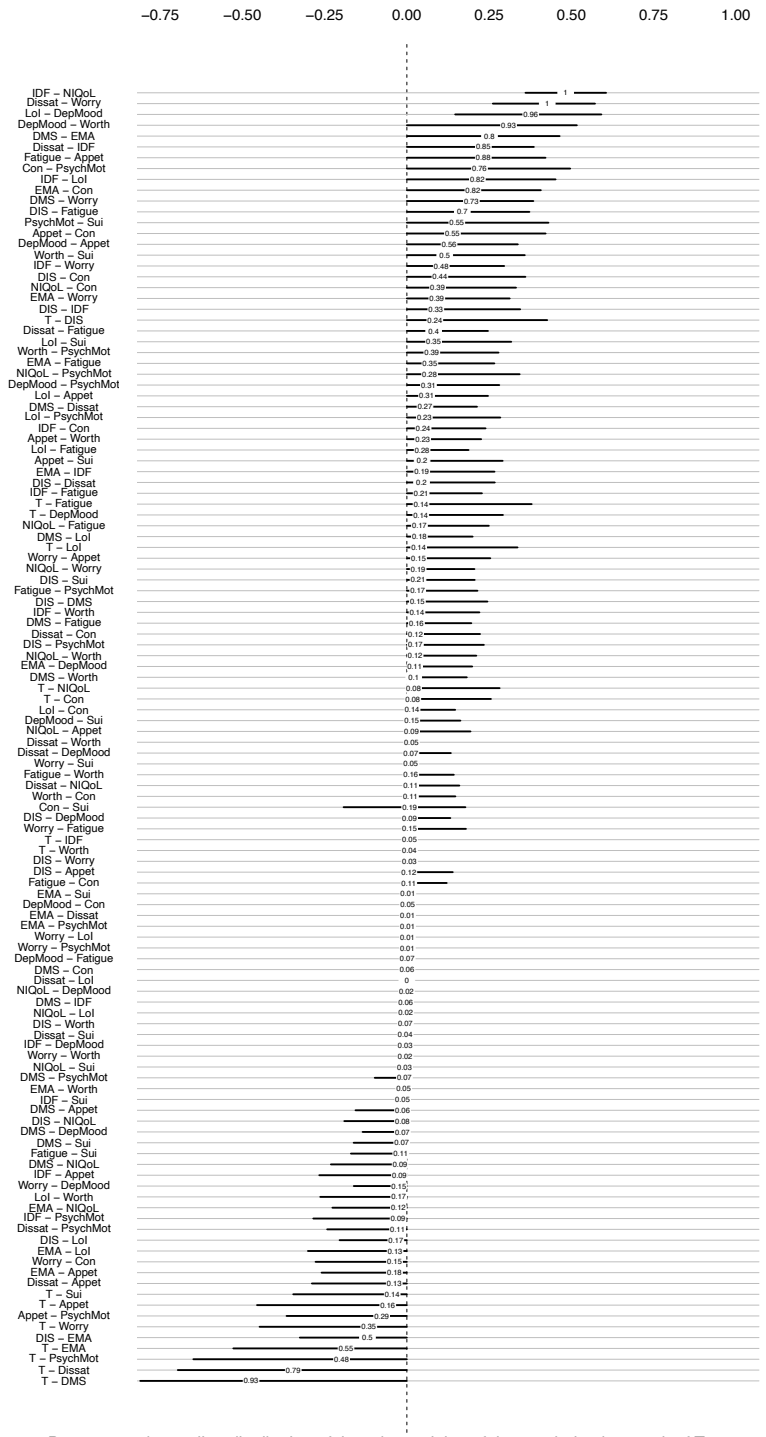
Bootstrapped sampling distribution of the edge weights of the regularized network of T6.



Bootstrapped sampling distribution of the edge weights of the regularized network of T7.



Bootstrapped sampling distribution of the edge weights of the regularized network of T8.



Bootstrapped sampling distribution of the edge weights of the regularized network of T9.

D

SUPPLEMENT TO 6: OVERLAPPING COMMUNITIES

Bootstrapping results indicated good accuracy of the estimated network parameters, see figure **??**. In addition, we calculated the correlation stability coefficient (CS), which represents the maximum proportion of participants that can be dropped while maintaining results that correlate at least 0.7 with the results obtained on the complete sample. We specifically focused on the stability of the strength and number of connections a node has (i.e., degree centrality) as this is most relevant for our community detection analyses. With a CS of 0.52, the stability exceeded the proposed cut-off of 0.5, suggesting good stability.

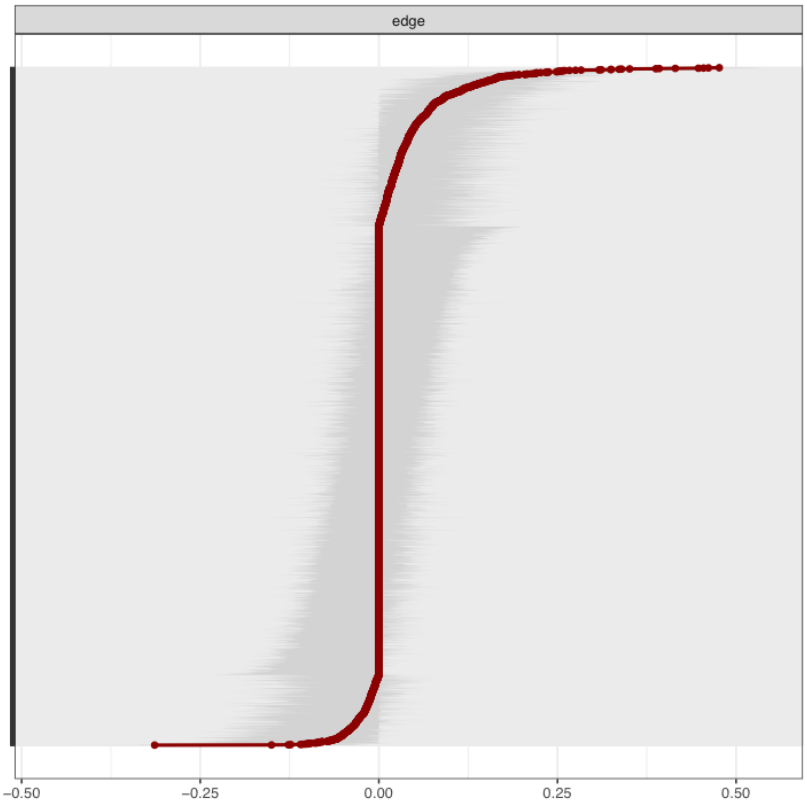


Figure D.1: Bootstrapped edge weights. The red line depicts point estimates of the edge weights in the reported network, the grey bars represent 95% confidence intervals.

		SCL-90 items and dimensions	communities																
			#1	#2	#3	#4	#5	#6	#7	#8	#9	#10	#11	#12	#13	#14	#15	#16	#17	#18
Depression	3	Repeated unpleasant thoughts that won't leave your mind	♦										♦							
	5	Loss of sexual interest or pleasure *																		
	14	Feeling low in energy or slowed down		♦					♦	♦	♦									
	15	Thoughts of ending your life		♦							♦							♦		♦
	19	Poor appetite									♦									
	20	Crying easily		♦								♦								
	22	Feeling of being trapped or caught		♦																
	26	Blaming yourself for things					♦											♦		
	29	Feeling lonely		♦																
	30	Feeling blue		♦									♦							
	31	Worrying too much about things					♦						♦							
	32	Feeling no interest in things		♦																
	51	Your mind going blank		♦																
	54	Feeling hopeless about the future		♦									♦							♦
	59	Thoughts of death or dying																		♦
	79	Feelings of worthlessness		♦														♦		
Anxiety	2	Nervousness or shakiness inside	♦																	
	17	Trembling	♦								♦									
	23	Suddenly scared for no reason									♦									
	33	Feeling fearful									♦									
	39	Heart pounding						♦												
	57	Feeling tensed or keyed up	♦							♦			♦							
	72	Spells of terror or panic	♦								♦									
	78	Feeling so restless you couldn't sit still *																		
	80	The feeling that something bad is going to happen to you																		♦
	86	Thoughts and images of a frightening nature									♦			♦						
Agoraphobia	13	Feeling afraid in open spaces or streets									♦									
	25	Feeling afraid to get out of your house alone									♦									
	47	Feeling afraid to travel on buses, subways or trains									♦									
	50	Having to avoid certain things, places, or activities because they frighten you									♦									
	70	Feeling uneasy in crowds such as shopping or at movies									♦				♦					
	75	Feeling nervous when you are left alone										♦								

		SCL-90 items and dimensions	communities																
			#1	#2	#3	#4	#5	#6	#7	#8	#9	#10	#11	#12	#13	#14	#15	#16	#17	#18
	82	Feeling afraid you will faint in public		♦							♦						♦			
Sleep difficulty	44	Trouble falling asleep							♦										♦	
	64	Awakening early in the morning							♦											
	66	Sleep that is restless or disturbed		♦					♦											
Somatization	1	Headaches	♦	♦	♦	♦														
	4	Faintness or dizziness			♦												♦			
	12	Pain in heart or chest						♦												
	27	Pains in lower back		♦																
	40	Nausea or upset stomach			♦			♦			♦									
	42	Soreness of muscles		♦																
	48	Trouble getting your breath		♦				♦												
	49	Hot or cold spells							♦											
	52	Numbness or tingling in parts of your body		♦				♦												
	53	A lumb in your throat										♦								
	56	Feeling week in parts of your body		♦																
	58	Heavy feelings in your arms or legs		♦																
Interpersonal sensitivity-mistrust	6	Feeling critical of others		♦							♦									
	7	The idea that someone else can control your thoughts		♦																
	8	Feeling others are to blame for most of your troubles		♦											♦					
	18	Feeling that most people cannot be trusted		♦																
	21	Feeling shy and uneasy with the opposite sex													♦					
	34	Your feelings being easily hurt														♦	♦			
	35	Other people being aware of your private thoughts		♦										♦						
	36	Feeling others do not understand you or are unsympathetic		♦												♦				
	37	Feeling that people are unfriendly or dislike you													♦	♦				
	41	Feeling inferior to others													♦			♦		
	43	Feeling that you are watched or talked about by others		♦												♦				
	61	Feeling uneasy when people are watching or talking about you									♦				♦	♦				
	68	Having ideas or beliefs that others do not share		♦							♦				♦					
	69	Feeling very self-conscious with others													♦					
	73	Feeling uncomfortable about eating or drinking in public		♦											♦					
	76	Others not giving you proper credit for achievements													♦	♦				
	83	Feeling that people will take advantage of you if you let them		♦											♦					
	88	Never feeling close to another person		♦																

		SCL-90 items and dimensions	communities																
			#1	#2	#3	#4	#5	#6	#7	#8	#9	#10	#11	#12	#13	#14	#15	#16	#17	#18
Acting-out hostility	11	Feeling easily annoyed or irritated		♦																
	24	Temper outbursts that you could not control				♦														
	63	Having urges to beat, injure or harm someone				♦														
	67	Having urges to break or smash things		♦		♦														
	74	Getting into frequent arguments				♦														
	81	Shouting or throwing things				♦														
Cognitive-performance deficits	9	Trouble remembering things					♦			♦										
	10	Worried about sloppiness or carelessness					♦													
	28	Feeling blocked in getting things done		♦																
	38	Having to do things very slowly to insure correctness		♦			♦													
	45	Having to double-check what you do					♦			♦									♦	
	46	Difficulty making decisions					♦													
	55	Trouble concentrating		♦						♦										
	65	Having to repeat the same actions, such as touching, counting, washing				♦													♦	
	71	Feeling everything is an effort		♦																
Unscaled SCL-90 items	16	Hearing voices that other people don't hear		♦		♦					♦									
	60	Overeating									♦									
	62	Having thoughts that are not your own		♦																
	77	Feeling alone even when you are with people		♦											♦					
	84	Having thoughts about sex that bother you a lot												♦			♦			
	85	The idea that you should be punished for your sins							♦					♦						
	87	The idea that something serious is wrong with your body																		♦
	89	Feelings of guilt												♦				♦		
	90	The idea that something is wrong with your mind									♦									

* Items #5 (Loss of sexual interest or pleasure; depression) and #78 (Feeling so restless you couldn't sit still; anxiety) are not associated with any community.

E

SUPPLEMENT TO 7: ADHD COMMUNITIES

E.1 SUPPLEMENTARY METHODS AND RESULTS

E.1.1 *Exploratory factor analysis*

To interpret the communities at a more detailed level, we conducted an exploratory factor analysis on the BFQ-C items. First we conducted a principal component analysis on all 65 items simultaneously. The five-factor factorial solution explained 41.1% of the total variance, similar to the original validation of the BFQ-C in which the five-factor solution explained 38.3% of the variance (Olivier & Hervé, 2015). To investigate the personality factors at a more detailed level we subsequently performed a principal component analysis on the items of each personality factor separately. We inspected the screen plot and the number of components with variance larger than 1: 3 for neuroticism, 4 for conscientiousness, 5 for agreeableness, and 6 for extraversion and openness. To be consistent across the personality factors, we choose to inspect the three-factor factorial solution for all personality factors. For all five personality factors, the three-factor solution explained more than 50% of the variance, ranging from 53.1% for Extraversion to 60.7% for Openness. Therefore we choose the three-factorial solution to interpret the identified communities at a more detailed level, see supplementary table E.1.

References

Olivier M, Herve M. The Big Five Questionnaire for Children (BFQ-C): A French validation on 8- to 14-year-old children. *Pers Individ Diff* 2015; **87:** 55–58.

E.2 SUPPLEMENTARY FIGURES AND TABLES

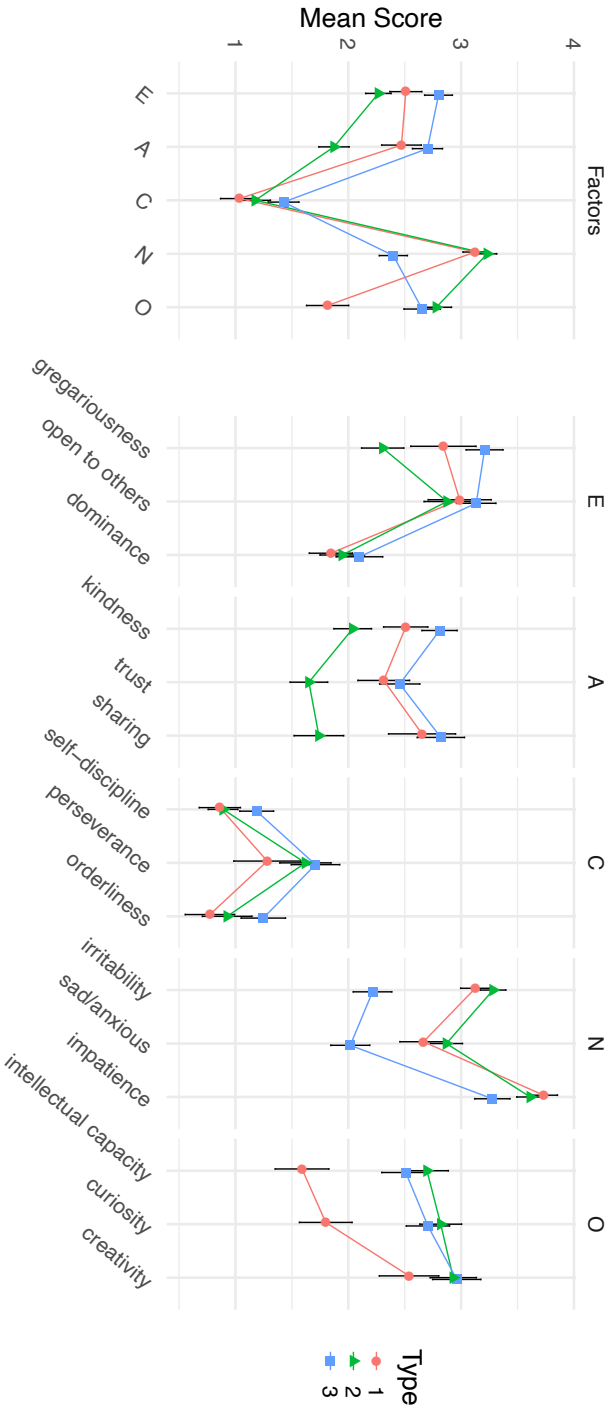


Figure E.1: Profiles identified based on the scores of the five personality factors: Extraversion, Agreeableness, Conscientiousness, Neuroticism, and Openness.

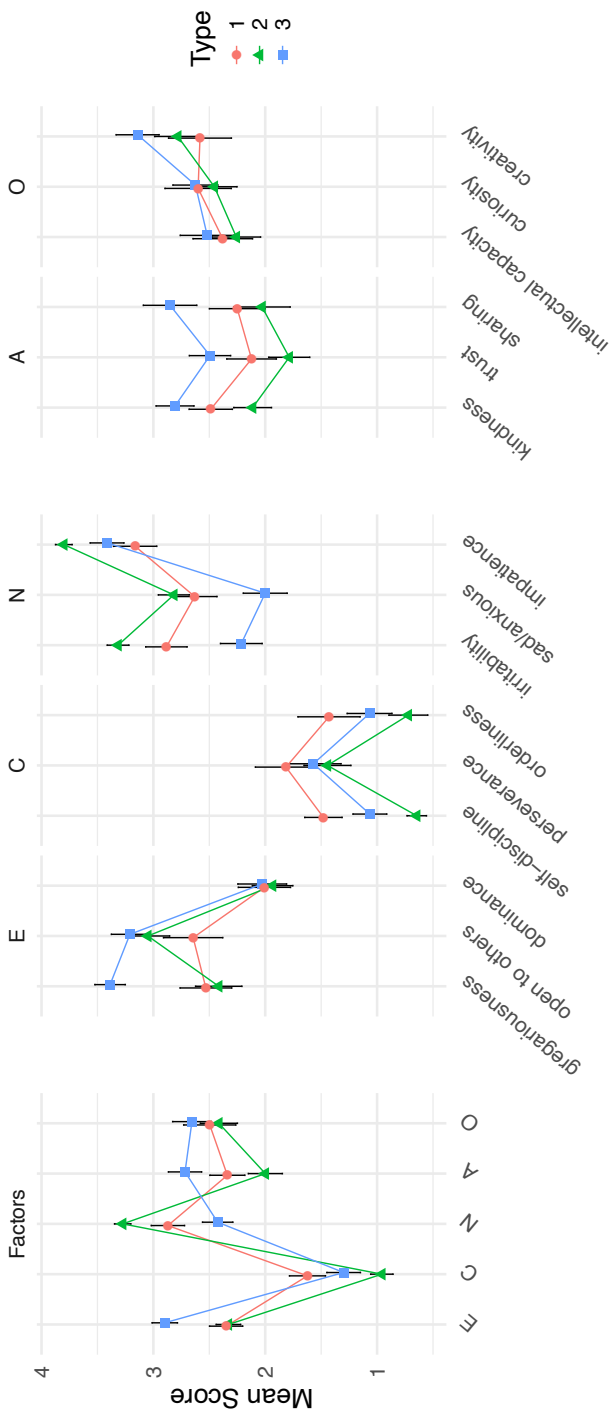


Figure E.2: Profiles identified based on the scores of the three personality factors that match the temperament dimensions included by Karalunas et al. (2014, 2018): Extraversion (E), Conscientiousness (C), and Neuroticism (N).

Table E.1: Exploratory factor loadings.

Items	Facets		
Extraversion	gregariousness	dominance	open to others
1. I like to spend time with other people	**0.85**	-0.04	-0.07
9. I like to compete	0.13	**0.60**	0.00
14. I like to be active	0.19	**0.54**	0.13
19. I like to be around others	**0.84**	0.04	-0.05
23. I can tell others what I think	0.05	-0.03	**0.82**
26. I say what I think	-0.06	0.02	**0.86**
35. I find things to do so I am not bored	0.13	-0.64	0.26
40. I like to talk with others	**0.64**	0.06	0.26
42. I am able to get people to agree with me	-0.09	**0.52**	0.37
50. Others listen and do what I say	0.27	**0.37**	0.07
55. I like to joke around	0.21	-0.04	**0.40**
57. I make friends easily	**0.74**	0.00	-0.02
63. I am happy and active	**0.56**	-0.02	0.10
Agreeableness	kindness	trust	sharing
2. I share my things	0.03	0.09	**0.85**
11. I am honest and kind	**0.83**	0.05	-0.13
13. I know when others need my help	**0.64**	-0.10	0.22
16. I like to give gifts	**0.52**	-0.16	0.25
21. I forgive	-0.13	**0.70**	0.19
27. I am nice to all my classmates	**0.60**	0.03	0.27
32. I treat others with kindness	**0.54**	0.16	0.34
38. I am polite when I talk to others	**0.67**	0.22	-0.23
45. I help classmates when they have trouble	**0.42**	-0.04	0.31
47. I trust others	0.04	**0.47**	0.38
51. I treat even people I dislike with kindness	0.09	**0.79**	-0.11
60. I think people are good and honest	0.09	**0.69**	0.06
64. I let other people use my things	0.03	0.02	**0.87**
Conscientiousness	self discipline	orderliness	persever-ance
3. I do my work carefully	0.22	**0.45**	0.39
7. I enjoy working hard	**0.78**	-0.03	0.01
20. I get involved and do my best	0.41	-0.06	**0.49**
22. I concentrate in class	**0.65**	-0.13	0.12
25. I check my homework many times	**0.53**	0.21	-0.06
28. I respect and follow rules	**0.68**	0.01	-0.16
34. I keep my appointments	0.27	0.29	**0.40**
37. My room is neat and organized	0.06	**0.84**	-0.16
44. I have to finish what I start	-0.11	0.19	**0.82**

Table E.1: (continued)

48. I keep my school things neat and organized	0.00	**0.73**	0.27
53. I finish homework before I play	**0.47**	0.14	-0.01
56. I pay attention to what I am doing	0.11	-0.28	**0.72**
65. I take care of my responsibilities	**0.69**	0.12	-0.02
Neuroticism	irritability	impatience	sad anxious
4. I get nervous	**0.77**	0.01	0.07
6. I am in a bad mood	**0.62**	-0.21	0.26
8. I get into heated arguments	**0.69**	0.27	-0.09
15. I get angry easily	**0.81**	-0.02	0.12
17. I argue with others	**0.72**	-0.11	-0.03
29. My feelings get hurt easily	0.35	0.09	**0.37**
31. I am sad	0.11	-0.11	**0.75**
39. I have to do things immediately	-0.11	**0.76**	0.13
41. I am not patient	0.19	**0.77**	-0.02
49. I lose my calm easily	**0.82**	0.10	-0.08
54. I get irritated with difficult things	0.45	**0.48**	-0.02
58. I cry	0.25	-0.13	**0.58**
61. I worry about silly things	-0.12	0.32	**0.74**
Openness	intellectual capacity	creativity	curiosity
5. I know a lot of things	0.43	-0.07	**0.49**
10. I daydream a lot	0.10	**0.70**	0.12
12. It is easy for me to learn	**0.87**	-0.03	-0.08
18. I am able to give correct answers	**0.79**	0.02	0.03
24. I like to read books	**0.54**	0.18	0.13
30. I understand directions immediately	**0.88**	0.05	-0.07
33. I like scientific TV shows	0.14	0.12	**0.67**
36. I like to watch the news and know what is going on	-0.14	-0.02	**0.82**
43. I make up new games and things to do	-0.06	**0.89**	-0.05
46. I am able to solve math problems	**0.67**	-0.09	-0.01
52. I like to learn new things	0.26	0.07	**0.57**
59. would like to travel, learn of other countries	-0.06	0.00	**0.74**
62. I understand things immediately	**0.72**	-0.05	0.18

Note. All loadings $\geq$ 0.40 are shown in bold font.

Table E.2: Mean (±SD) on the Big Five personality factor scores and EFA subscales for the three types.

Characteristics	Time	Type 1	Type 2	Type 3	F(2,175)	Post-hoc
Big Five Personality Scores						
Extraversion	T0	2.55 (0.45)	2.39 (0.52)	2.68 (0.56)	5.65*	3>2
	T1	2.28 (0.52)	2.40 (0.54)	2.74 (0.45)	12.45*	3>1,2
Agreeableness	T0	2.50 (0.50)	1.82 (0.50)	2.81 (0.49)	71.39*	3>1>2
	T1	2.65 (0.37)	2.05 (0.45)	2.90 (0.48)	66.62*	3>1>2
Neuroticism	T0	3.07 (0.38)	3.18 (0.40)	2.44 (0.56)	48.60*	1,2>3
	T1	3.10 (0.43)	3.07 (0.43)	2.12 (0.57)	76.72*	1,2>3
Consciousness	T0	1.11 (0.56)	1.15 (0.52)	1.42 (0.61)	5.49*	3>1,2
	T1	1.31 (0.64)	1.24 (0.54)	1.64 (0.63)	8.10*	3>1,2
Openness to Experience	T0	1.82 (0.60)	2.73 (0.62)	2.52 (0.72)	30.23*	2,3>1
	T1	2.11 (0.60)	2.88 (0.52)	2.81 (0.66)	23.30*	2,3>1
Big Five Personality Subscales						
Gregariousness	T0	2.85 (0.87)	2.41 (0.84)	3.15 (0.72)	15.02*	1,3>2
	T1	2.60 (0.64)	2.39 (0.63)	3.22 (0.55)	32.29*	3>1,2
Open to others	T0	3.02 (0.81)	2.91 (0.86)	3.09 (0.77)	0.82	
	T1	2.48 (0.94)	2.72 (0.87)	2.75 (0.82)	1.27	
Dominance	T0	1.82 (0.69)	2.19 (0.77)	1.86 (0.84)	4.33*	2>1,3
	T1	1.85 (0.64)	2.41 (0.75)	2.29 (0.70)	7.66*	2,3>1
Kindness	T0	2.52 (0.59)	1.99 (0.65)	2.91 (0.61)	39.25*	3>1>2
	T1	2.76 (0.54)	2.17 (0.53)	3.04 (0.56)	42.01*	3>1>2
Trust	T0	2.38 (0.74)	1.56 (0.59)	2.57 (0.69)	44.54*	1,3>2
	T1	2.48 (0.61)	1.80 (0.78)	2.63 (0.67)	24.39*	1,3>2
Sharing	T0	2.68 (0.87)	1.72 (0.92)	2.90 (0.82)	34.74*	1,3>2
	T1	2.64 (0.84)	1.91 (0.72)	2.95 (0.88)	27.08*	1,3>2
Self-discipline	T0	0.90 (0.62)	0.88 (0.54)	1.20 (0.62)	5.97*	3>1,2
	T1	1.19 (0.58)	1.01 (0.54)	1.54 (0.69)	12.24*	3>1,2
Perseverance	T0	1.43 (0.94)	1.61 (0.94)	1.64 (0.93)	0.62	
	T1	1.47 (1.09)	1.75 (0.84)	1.84 (0.94)	1.90	
Orderliness	T0	0.82 (0.76)	0.88 (0.79)	1.28 (0.91)	5.48*	3>1,2
	T1	1.15 (0.91)	0.81 (0.87)	1.30 (0.79)	5.66*	3>2
Irritability	T0	3.09 (0.42)	3.29 (0.44)	2.17 (0.72)	75.93*	1,2>3
	T1	3.05 (0.55)	3.10 (0.53)	1.85 (0.78)	72.96*	1,2>3
Sad/anxious	T0	2.58 (0.68)	2.71 (0.68)	2.18 (0.81)	9.55*	1,2>3
	T1	2.73 (0.75)	2.44 (0.75)	1.73 (0.79)	24.52*	1,2>3
Impatience	T0	3.71 (0.43)	3.57 (0.53)	3.31 (0.64)	7.14*	1,2>3
	T1	3.36 (0.50)	3.41 (0.47)	2.55 (0.64)	46.40*	1,2>3
Intellectual capacity	T0	1.51 (0.74)	2.69 (0.80)	2.53 (0.84)	28.87*	2,3>1
	T1	1.87 (0.68)	2.85 (0.67)	2.68 (0.85)	21.70*	2,3>1
Curiosity	T0	1.84 (0.80)	2.71 (0.79)	2.77 (0.78)	19.48*	2,3>1
	T1	2.18 (0.94)	2.91 (0.68)	2.90 (0.85)	11.56*	2,3>1
Creativity	T0	2.72 (0.88)	2.87 (0.88)	2.93 (0.88)	0.69	
	T1	2.63 (1.01)	2.88 (0.84)	2.96 (0.90)	1.64	

Table E.3: Mean (±SD) on the Big Five personality factor scores for the three ADHD types compared with a normative control sample.

Characteristics	Normative sample	Type 1	Type 2	Type 3	F(3,349)	Post-hoc
Big Five Personality Scores						
Extraversion	2.81 (0.53)	2.55 (0.45)	2.39 (0.52)	2.68 (0.56)	11.69 ***	Norm>1,2
Agreeableness	2.74 (0.53)	2.50 (0.50)	1.82 (0.50)	2.81 (0.49)	62.97 ***	Norm>1,2
Neuroticism	1.63 (0.80)	3.07 (0.38)	3.18 (0.40)	2.44 (0.56)	123.69 ***	Norm>1,2,3
Consciousness	2.41 (0.66)	1.11 (0.56)	1.15 (0.52)	1.42 (0.61)	109. 37 ***	Norm>1,2,3
Openness to Experience	2.77 (0.57)	1.82 (0.60)	2.73 (0.62)	2.52 (0.72)	26.31 ***	

F

SUMMARY

Insomnia is a very common mental health problem. One in every three adults suffers from sleep problems such as difficulty falling asleep, difficulty maintaining asleep, or early morning awakenings. And for one in every ten people these problems are chronic. They suffer from sleep problems at least three nights a week, for at least three months, and it interferes with their daily functioning. These people suffer from insomnia disorder.

In addition to the discomfort that insomnia can cause at night and during the day, suffering from insomnia is also a risk factor for many medical and mental disorders. For example, insomnia increases the risk of depression, one of the most common and burdensome illnesses of our time. Insomnia can therefore have major health-consequences, both at present and in the future. Accordingly, it is very important to be able to understand who the people suffering from insomnia are. How do they differ from good sleepers? And why do some people with insomnia develop a depression, while others do not? To answer these questions will help us to identify, at an early stage, the people that are at risk, and to optimize the available treatments for insomnia.

Unfortunately, it proved difficult to answer these questions. This was mostly because, over the years, many findings on insomnia turned out to be inconsistent. While one research group found a certain brain circuit that seemed important for insomnia, this could not be replicated in a subsequent study and a different brain circuit appeared to be of importance. This was not only the case for brain circuits, but also in other areas such as cognition, mood, life history, family history and the microstructure of sleep. These inconsistencies hinder a better understanding of how insomnia is developed and maintained. At the same time, these inconsistencies may point to something else: it may be true that for some people with insomnia one brain circuit is important, while for a second group another brain circuit is important. In other words, perhaps these inconsistent findings are not inconsistencies, but point to the existence of different subgroups of people with insomnia.

The idea that insomnia may not be one homogeneous group, but consists of several subgroups, is the basis of the first part of this dissertation. This idea of subgroups within insomnia, however, is not new. Over the years, many different subgroups of insomnia have been proposed. For example, there was the idea of classifying people according to their dominant sleep complaint: difficulty falling asleep *versus* difficulty sleeping through the night *versus* problems with waking up too early. Unfortunately, this classification did not appear to be robust: even within a few months, people's dominant sleep complaint could change. This variability is problematic as we aim to find subgroups that are robust over time, so that we can ultimately understand the mechanisms behind insomnia better

in order to optimize its treatment. This ultimate goal becomes challenging when the types change over time. In that case, it suddenly matters whether someone comes to seek help in January, when difficulty falling asleep is the main complaint; or in June, when it may have turned into difficulty maintaining asleep being the dominant sleep complaint. An important condition in our research into subtypes of insomnia was therefore that they would be stable over time.

For this reason, we looked not only at the sleep problems themselves, but also at all kinds of other characteristics that may be important in the development and maintenance of insomnia: from personality traits to life-history, and from worrying and ruminating to the experience of happiness. All these characteristics have been shown to be relatively stable within persons and over time. Someone who tends to worry a lot, often has this tendency throughout his or her life. In this way, we had a very broad (multivariate) approach, in which we investigated whether different profiles might be captured within all these characteristics. Following this perspective, people's sleep problems may be the same, but it is actually the context in which the problems are developed and maintained that differs. It is thus not a single characteristic that is relevant to the different types, but rather a whole *system* in which the entire profile is of importance.

Based on this perspective, we collected a lot of data from many different people. This was made possible through the online platform of the Dutch Sleep Registry (www.slaapregister.nl), which was set up precisely for this reason. On the registry, anyone can create an account, which then gives access to many different questionnaires. From a very large group of more than 4000 good and bad sleepers we collected information on up to 34 different characteristics. Within the group of bad sleepers we found that, based on these characteristics, it is not one homogeneous group, but rather a heterogeneous group that can be better divided into five subgroups. Five types of insomnia: (1) a highly distressed type that experiences both many negative and very few positive emotions; two moderately distressed types that can be distinguished from each other because type (2) is mainly sensitive to stress, while type (3) is characterised by a lack of positive emotions; and two groups that are similar to people without insomnia in many respects, but one type (4) reacts strongly to life events and the other type (5) shows very little positive and negative emotions. A follow-up measurement showed that, even after a number of years, most people still belonged to the same subtype. The subtypes thus appeared to be stable over time.

Next, the most important question was whether these subtypes are clinically relevant: can we actually meaningfully distinguish people with insomnia from each other based on these subtypes? We made a small start in this respect and found, for example, that the development of sleep problems throughout the course of life differed greatly between the various types; and that cognitive behavioural therapy may have a different effect on the various types. One finding that is specifically important for the rest of this dissertation was that

the degree of depression problems that people with insomnia reported, both in the past and in the present, differed greatly depending on the type to which they belonged. While more than one-half of the people with type 1 had ever had a depression, and more than one-third had current mood problems; for type 4 this was less than 10 and 1 percent, respectively. Perhaps we can thus use these subtypes to identify people with insomnia who are at greater risk of developing a depression. By identifying the people with the highest risk at an early stage, we may even be able to prevent the depression.

This link between insomnia and depression formed the basis for the second part of this dissertation. A lot of research has already been done into this relationship. For example, it has been shown repeatedly that people with insomnia are at a higher risk for developing a depression; that 80% of people with depression also suffer from sleep problems (co-morbidity); and that when people with co-morbid insomnia and depression problems are treated for their insomnia, this not only reduces the sleep problems but also the depression problems. All these studies thus highlight the strong relationship between the two disorders. However, if we critically and carefully consider what it means to get a diagnosis of insomnia or depression, the interpretation of these results becomes more complex. Insomnia is after all not only a disorder of the night, but also a disorder of the day. In order to diagnose insomnia, a person has to suffer both from sleep problems at night and from reduced functioning during the day. Similarly, a diagnosis of depression can also include sleep problems. This strong overlap in symptomatology therefore raises the question of how we can meaningfully distinguish between these two disorders. Can this overlap in symptoms be an alternative explanation for the strong link that has been found between the two disorders? Can insomnia be a risk factor for depression simply because it is a symptom of depression?

In two studies we tried to re-examine the link between insomnia and depression, while taking this complexity of symptom overlap into account. We did so by investigating insomnia and depression not as two separate 'disorders', but rather as networks of interrelated symptoms. In this way, the direct relationships between symptoms are at the heart of the system and we can investigate the role of specific complaints in this system of symptoms. First of all, we investigated whether sleep problems increase the risk of depression, when viewed from this system's perspective. Instead of looking at insomnia as a disorder, in which people already have to suffer from daytime problems as well, we looked at the system of daytime and nighttime complaints and identified which specific complaints within that system are predictive for the development of a depression. Five complaints were found to increase the risk of depression, including difficulties falling asleep. This finding confirms that sleep problems increase the risk of depression, even if we take the relationship between the various day and nighttime complaints into account. This finding is important in identifying people who are at increased risk for developing a depression, such that we can ultimately prevent rather than treat depression.

At present, however, depression is very common, and often in combination with insomnia. In this respect, the results that point to the potential role of insomnia for its treatment are promising; as the successful treatment of insomnia seems to also reduce the symptoms of depression. At the same time, the question remained: do these effects really originate from the treatment of sleep problems at night? Or does the treatment possibly focus on the daytime complaints, such as worry and sad mood, both symptoms being part of insomnia as well? Again, we did not look at the individual symptoms or disorders, but at the system of day and nighttime complaints. Within this system, we investigated which specific complaints were targeted by the treatment using a new analysis that we introduced, called *Network Intervention Analysis*. This new analysis showed that indeed mainly sleep problems were tackled by the treatment; and specifically problems with sleeping through the night and early morning awakenings. So it does seem to be the case that the successful treatment of sleep problems is a driving force for the improvement of the depression problems. These studies together thus indicate that insomnia is of primary importance in predicting, preventing and alleviating depression.

Although the questions that are central to this dissertation are not novel, the way in which we investigated them is. Instead of merely focusing on the sleep problems to find subtypes, we broadened our perspective. This turned out to yield stable subtypes and the first results in terms of their clinical utility are promising. We moreover investigated the relationship between insomnia and depression from a new perspective, that is, as a system of symptoms. These investigations offer new starting points and suggest that the path from insomnia to depression (via problems with falling asleep) does not have to be the same as the path back (via problems with maintaining asleep and early morning awakenings). Together, all studies in this dissertation have an important common denominator: by changing our perspective, from single symptoms to complex systems, we can learn a lot about psychopathology in general, and the link between insomnia and depression in particular.

G

NEDERLANDSE SAMENVATTING

Slapeloosheid is een veelvoorkomend probleem. Eén op de drie volwassenen heeft last van slaapklachten als moeite met inslapen, moeite met doorslapen, of te vroeg wakker worden. En voor één op de tien mensen zijn deze problemen chronisch. Zij hebben ten minste drie nachten per week last van slaapproblemen, voor ten minste drie maanden lang, waarbij het hun dagelijks functioneren belemmert. Deze mensen lijden aan insomnie.

Naast het ongemak dat insomnie in de nacht en ook overdag kan veroorzaken, is het lijden aan insomnie ook nog een risicofactor voor vele medische en mentale aandoeningen. Zo verhoogt insomnie bijvoorbeeld het risico op depressie, één van de meest voorkomende en belastende problemen van het moment. Het lijden aan insomnie kan dus grote gevolgen hebben voor iemands gezondheid, zowel op het moment zelf, als in de toekomst. Daarom is het heel belangrijk dat we goed in kaart kunnen brengen wie de mensen zijn die aan insomnie lijden. Hoe verschillen zij van goede slapers? En waarom ontwikkelen sommige mensen met slapeloosheid een depressie, terwijl anderen daarvan bespaard blijven? Een antwoord op deze vragen zal ons helpen om vroegtijdig risicogroepen te identificeren en de behandeling voor insomnie te optimaliseren.

Toch bleek een antwoord op deze vragen niet zo makkelijk te geven. Dit kwam voornamelijk doordat er nogal wat inconsistente bevindingen waren over de jaren heen. Vond één onderzoeksgroep een bepaald hersencircuit dat van belang leek voor insomnie, kon dit in een volgende studie niet gerepliceerd worden en bleek juist een ander hersencircuit van belang. Dit was het geval niet alleen voor hersencircuits, maar ook op andere vlakken zoals cognitie, stemming, levensgeschiedenis, familiegeschiedenis en de microstructuur van slaap. Deze inconsistenties maken het lastig om beter te begrijpen hoe insomnie ontstaat, en in stand gehouden wordt. Tegelijkertijd wijzen deze inconsistenties misschien wel op iets anders: wellicht klopt het dat bij sommige mensen met insomnie het ene hersencircuit van belang is, terwijl voor een tweede groep een ander hersencircuit van belang is. Met andere woorden, misschien zijn deze inconsistente bevindingen geen tegenstrijdigheden, maar wijzen ze op het bestaan van verschillende subgroepen van mensen met insomnie.

Het idee dat insomnie misschien niet één homogene groep is, maar juist uit verschillende subgroepen bestaat, staat aan de basis van het eerste deel van dit proefschrift. Dit idee is echter niet nieuw. Over de jaren heen zijn er veel verschillende subgroepen van insomnie voorgesteld. Zo was er bijvoorbeeld het idee om mensen in te delen op basis van hun dominante slaapklacht: moeite met inslapen *versus* moeite met doorslapen *versus* te vroeg wakker worden. Deze indeling bleek helaas niet robuust: zelfs binnen een tijdsbestek van een aantal maanden kon de dominante slaapklacht van mensen al sterk

veranderen. Deze veranderlijkheid is problematisch aangezien we subgroepen willen vinden die robuust zijn over de tijd, zodat we meer kunnen begrijpen over de mechanismen achter insomnie, en de behandeling er voor kunnen optimaliseren. Bij veranderlijke typen wordt dat erg lastig. Dan maakt het opeens uit of iemand in januari hulp komt zoeken, wanneer moeite met inslapen de voornaamste klacht is; of in juni, wanneer dat misschien is overgegaan in moeite met doorslapen. Een belangrijke voorwaarde binnen ons onderzoek naar subtypen van insomnie was dan ook dat deze stabiel moesten zijn over de tijd.

Daarom keken wij in ons onderzoek niet alleen naar de slaapklachten zelf, maar ook naar allerlei andere eigenschappen die mogelijk van belang zijn bij het ontstaan van insomnie: van karaktereigenschappen tot levensgeschiedenis en van piekeren en rumineren tot het ervaren van geluk. Al deze eigenschappen zijn aangetoond relatief stabiel te zijn binnen personen en over de tijd heen. Iemand die geneigd is veel te piekeren, heeft die neiging vaak gedurende zijn of haar leven. Op deze manier hadden we een hele brede (multivariate) aanpak, waarin we keken of er binnen al deze eigenschappen misschien verschillende profielen te vinden waren. Het idee was dat de slaapklachten van mensen mogelijk wel hetzelfde kunnen zijn, maar dat mensen kunnen verschillen in de context waarbinnen de slaapklachten zijn ontstaan en in stand gehouden worden. Vanuit deze gedachten is het dus niet één enkele eigenschap die relevant is voor de verschillende typen, maar juist een heel *systeem* waarbij het hele profiel van belang is.

Vanuit deze achterliggende gedachten verzamelden we veel data van veel verschillende mensen. Dit was mogelijk door het online platform van het Nederlands Slaapregister (www.slaapregister.nl) wat precies om deze reden is opgezet. Iedereen kan daar een account op aanmaken, wat toegang geeft tot veel verschillende vragenlijsten. Zo hadden we van een hele grote groep van meer dan 4000 goede en slechte slapers informatie over tot wel 34 verschillende eigenschappen. Binnen de groep slechte slapers vonden we vervolgens op basis van deze eigenschappen dat het niet één homogene groep is, maar dat de groep beter onderverdeeld kan worden in vijf groepen. Vijf typen van insomnie: type (1) die zowel veel negatieve als erg weinig positieve emoties ervaart; twee groepen die iets minder negatief scoren dan de eerste groep en van elkaar onderscheden worden doordat type (2) voornamelijk gevoelig is voor stress, terwijl type (3) gekenmerkt wordt door een sombere inslag; en twee groepen die op veel eigenschappen eigenlijk lijken op mensen zonder slapeloosheid, maar waarvan één type (4) sterk reageert op levensgebeurtenissen en het andere type (5) juist erg weinig positieve en negatieve emoties laat zien. Uit een vervolgmeting bleek dat de meeste mensen, zelfs na een aantal jaar, nog steeds tot hetzelfde subtype behoorden. De subtypen bleken dus stabiel over de tijd.

De belangrijkste vervolgvraag was nu of deze deze subtypen klinisch relevant zijn: kunnen we op basis van deze subtypen mensen met insomnie inderdaad op een betekenisvolle manier van elkaar onderscheiden en vervolgens behandelen? We maakten hiermee een begin en vonden bijvoorbeeld dat de ontwikkeling van de slaapklachten door de levensloop heen sterk verschilde tussen de verschil-

lende typen; en dat cognitieve gedragstherapie mogelijk verschillend effect heeft voor de verschillende typen. Eén bevinding die specifiek van belang is voor de rest van dit proefschrift was dat de mate van depressieklachten die mensen met insomnie rapporteerden, zowel in het verleden als heden, sterk verschilden afhankelijk van het type waar iemand toe behoorde. Had van de mensen met type 1 meer dan de de helft ooit een depressie gehad en kampte meer dan een derde met huidige stemmingsproblemen, was dit bij type 4 respectievelijk nog geen 10 en 1 procent. Misschien kunnen we middels deze subtypen dus ook de mensen met slapeloosheid identificeren die een verhoogd risico hebben voor het ontwikkelen van een depressie. En door al vroegtijdig de mensen te identificeren die het hoogste risico lopen, kunnen we de depressie misschien zelfs voorkomen

Deze link tussen insomnie en depressie vormde de basis voor het tweede deel in dit proefschrift. Er is al veel onderzoek gedaan naar deze samenhang. Zo blijkt dat mensen met insomnie een sterk verhoogd risico hebben voor het ontwikkelen van een depressie; dat 80% van de mensen met een depressie ook last heeft van slaapklachten (co-morbiditeit); en dat wanneer mensen met co-morbide insomnie- en depressieklachten behandeld worden voor hun insomnie, dat dan niet alleen de slaap- maar óók de depressieklachten verminderen. Al deze onderzoeken wijzen dus op de sterke samenhang van beide stoornissen. Wanneer we echter kritisch en in detail kijken naar wat het betekent om een diagnose van insomnie of depressie te krijgen, dan wordt het beeld wat complexer. Insomnie is namelijk niet alleen een stoornis van de nacht, maar ook van de dag. Voor een diagnose van insomnie moet iemand zowel aan slaapklachten in de nacht als aan verminderd functioneren overdag lijden. En onder een diagnose van depressie valt ook het symptoom 'slaapproblemen'. Deze sterke overlap in symptomatologie roept dan ook de vraag op hoe we deze stoornissen op een betekenisvolle wijze uit elkaar kunnen houden. En vormt deze overlap in symptomen niet een alternatieve verklaring voor de sterke link die is gevonden? Is insomnie niet een risico factor van depressie simpelweg omdat het een symptoom is van depressie?

In twee onderzoeken probeerden we de link tussen insomnie en depressie opnieuw te onderzoeken, onderwijl rekening houdend met die complexiteit in symptoom overlap. Dit deden we door insomnie en depressie niet als twee afzonderlijke 'stoornissen' te onderzoeken, maar juist als netwerken van gerelateerde symptomen. Op deze manier staan de directe relaties tussen symptomen centraal en kunnen we in het systeem van symptomen onderzoeken welke rol specifieke klachten hebben. Allereerst onderzochten we of slaapklachten het risico op depressie verhogen, ook vanuit dit systeem bezien. Dus in plaats van dat we keken naar insomnie al stoornis, waarbij mensen dus al aan dagklachten moeten voldoen, keken we naar het systeem van dag- en nachtklachten en identificeerden we welke specifieke klachten binnen dat systeem voorspellend zijn voor het ontwikkelen van een depressie. Vijf klachten bleken het risico op depressie te verhogen, waaronder moeite met in slaap vallen. Dit bevestigt dus dat slaapklachten het risico op een depressie verhogen, zelfs als we rekening

houden met de samenhang tussen de verschillende dag- en nachtklachten. Deze bevinding is van belang in het identificeren van mensen met een verhoogd risico op depressie. Uiteindelijk zou de depressie daarmee mogelijk *voorkomen* kunnen worden.

Op dit moment komt depressie echter heel veel voor, en ook vaak samen met insomnie. Veelbelovend zijn de resultaten die wijzen op de rol van insomnie; en hoe het succesvol behandelen van insomnie ook de depressieklachten verminderd. Tegelijkertijd was ook hier de vraag: gaan deze effecten echt via het behandelen van de slaapklachten in de nacht? Of richt de behandeling zich mogelijk op de dagklachten, zoals zorgen maken en sombere stemming, welke ook beiden onderdeel zijn van insomnie. Opnieuw keken we dus niet naar de individuele klachten, of stoornissen, maar naar het systeem van dag- en nachtklachten. Binnen dit systeem onderzochten we welke specifieke klachten door de behandeling werden aangepakt middels een nieuwe analyse die we introduceerden, de *Netwerk Interventie Analyse*. Uit deze nieuwe analyse bleek dat inderdaad voornamelijk slaapklachten aangepakt werden door de behandeling; en dan specifiek moeite met doorslapen en te vroeg wakker worden. Het lijkt dus inderdaad zo te zijn dat het succesvol behandelen van de slaapklachten een drijvende kracht is achter het verbeteren van de depressieklachten. Deze onderzoeken laten tezamen zien dat insomnie dus van primair belang lijkt te zijn in het voorspellen, voorkomen en verlichten van depressie.

De vragen die centraal staan in dit proefschrift waren niet nieuw. De manier waarop we naar deze vragen keken wel. In plaats van ons te richten op de slaapklachten van insomnie voor het vinden van subtypen, verbreedden we ons perspectief. Dit bleek stabiele subtypen op te leveren en de eerste resultaten naar hun klinische relevantie zijn veelbelovend. Ook de samenhang tussen insomnie en depressie bekeken we vanuit een nieuw perspectief, namelijk als systeem van klachten. Dit onderzoek biedt nieuwe aanknopingspunten en wijst erop dat de weg van insomnie naar depressie toe (via problemen met inslapen), niet dezelfde hoeft de zijn als de weg terug (via problemen met doorslapen en te vroeg wakker worden). En daarmee hebben alle onderzoeken in dit proefschrift een belangrijke gemeenschappelijke deler: dat we door ons perspectief te veranderen, van enkelvoudige symptomen naar complexe systemen, heel veel kunnen leren over psychopathologie in het algemeen, en de link tussen insomnie en depressie in het bijzonder.

I

PUBLICATIONS

PAPERS

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* shared first authorship

APPLICATION

We developed a shiny-app web-application that can be used to automatically compute someone's insomnia subtype based on the Insomnia Type Questionnaire that we have created: `https://tfblanken.shinyapps.io/itqapp/`.

MEDIA

Our paper on insomnia subtypes got a lot of media coverage across the world: From China to Australia and from Mexico to Ukrain, the paper was covered in 13 languages in 22 different countries. All media coverage can be found here: `https://tinyurl.com/MediaInsomniaSubtypes`. Some highlights:

- Interview with Neurology live (video in English): `https://www.neurologylive.com/conferences/esrs-2018/tessa-blanken-msc-identification-of-robust-clinically-relevant-insomnia-subtypes`
- Interview with NEMO kennislink (text in Dutch): `https://www.nemokennislink.nl/publicaties/vijf-typen-slapeloosheid-verborgen-in-karaktereigenschappen/`
- Interview with Psychology Magazine (text in Dutch): `https://www.psychologiemagazine.nl/artikel/dit-zijn-de-5-typen-slechte-slapers/`
- The paper reached a very large audience through r/science: `https://www.reddit.com/r/science/comments/ahruy8/there_are_five_types_of_insomnia_each_with_its/`